PROTOCOL FOR THE TREATMENT OF BENZODIAZEPINE WITHDRAWAL

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DM, FRCP

BENZODIAZEPINES:

HOW THEY WORK & HOW TO WITHDRAW

aka

The Ashton Manual

Revised August 2002

Includes 2011, 2012 & 2013 Supplements

Medical Research Information

From a Benzodiazepine

Withdrawal Clinic

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BENZODIAZEPINES: HOW THEY WORK AND HOW TO WITHDRAW

(aka The Ashton Manual)

- PROTOCOL FOR THE TREATMENT OF BENZODIAZEPINE WITHDRAWAL
- Medical research information from a benzodiazepine withdrawal clinic

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CONTENTS PAGE

INTRODUCTION

THE ASHTON MANUAL SUPPLEMENT, APRIL 2011

IMPORTANT MESSAGE FROM PROFESSOR ASHTON, JANUARY 2007

Professor Ashton would like to draw attention to the following points which are mentioned in the manual but not always heeded by doctors or patients:

1. It is worth pointing out to your prescriber that the withdrawal schedules provided in the manual are only intended as *general guides*. **The rate of tapering should never be rigid but should be flexible and controlled by the patient, not the doctor, according to the patient's individual needs which are different in every case.**
2. The decision to withdraw is also the **patient's decision** and **should not be forced by the doctor**.
3. Note that alcohol acts like benzodiazepines and should be used, if at all, in strict moderation as advised in this manual.
4. Antibiotics for some reason, sometimes seem to aggravate withdrawal symptoms. However, one class of antibiotics, the quinolones, actually displace benzodiazepines from their binding sites on GABA-receptors. These can precipitate acute withdrawal in people taking or tapering from benzodiazepines. It may be necessary to take antibiotics during benzodiazepine withdrawal but if possible the quinolones should be avoided. (There are at least six different quinolones - ask your doctor if in doubt).

C. H. Ashton, January 2007

FOREWORD TO REVISED EDITION, AUGUST 2002

This edition contains some new material which I have added in response to requests and queries from readers in many countries including Europe, North America, Australia, New Zealand, South Africa and India. Additions include further information about withdrawal of antidepressant drugs, some advice for older or "elderly" people, and a mention of complementary, non-drug, techniques helpful in benzodiazepine withdrawal. There is also an epilogue outlining areas where further action about benzodiazepines - education, research and facilities for long-term users - is urgently needed. I am glad that this monograph has been helpful to people all over the world and am grateful for the many thanks I have received. I hope also that it will encourage professionals and others to undertake properly controlled trials aimed at improving the management of benzodiazepine withdrawal. This booklet is surely not the last word on the subject.

Heather Ashton
Newcastle upon Tyne
August 2002

FOREWORD 2001

These chapters were written by request in 1999 for readers in the USA concerned about the problems associated with long-term benzodiazepine use. Inquiries from Canada, Australia and the UK have suggested that the advice in the manual might be of help to a wider audience. Accordingly, some additions have now been made, particularly for readers in the UK.

A limited list of benzodiazepines that can be prescribed on the National Health Service was introduced in the UK in 1985. These include diazepam, chlordiazepoxide, lorazepam and oxazepam for anxiety; nitrazepam and temazepam for insomnia. Triazolam was originally on the list but was later withdrawn. Other sleeping pills now available on the NHS include the benzodiazepines loprazolam and lormetazepam and two drugs, zopiclone and zolpidem, which although not benzodiazepines, act in the same way and have the same adverse effects including dependence and withdrawal reactions. Information about benzodiazepines not included in the first US edition, and suggested withdrawal schedules for chlordiazepoxide, oxazepam and zopiclone have been added here.

Unfortunately, the benzodiazepine saga is far from over. Despite the fact that benzodiazepines are only recommended for short-term use, there are still about half a million long-term benzodiazepine users in the UK who have often been prescribed benzodiazepines for years. Many of these people have problems with adverse effects including dependence and withdrawal reactions, for which they receive little advice or support. The problem is even greater in countries (Greece, India, South America and others) where benzodiazepines are available over the counter. Because of widespread prescribing and easy availability, benzodiazepines have now, in addition, entered the "drug scene". They are taken illicitly in high doses by 90% of polydrug abusers world-wide, unleashing new and dangerous effects (AIDS, hepatitis, and risks to the next generation) which were undreamt of when they were introduced into medicine as a harmless panacea nearly 50 years ago.

I hope this booklet will provide information of value to benzodiazepine users unable to find advice elsewhere and perhaps raise awareness in the medical profession about the dangers of excessive or long-term benzodiazepine prescribing. The main credit for any use this monograph may be should go to Geraldine Burns in the USA, Rand M Bard in Canada, and Ray Nimmo and Carol Packer in the UK for their energy, enthusiasm and expertise in producing and distributing this booklet and making it available to people on the Internet throughout the world.

Heather Ashton
January 2001

ABOUT PROFESSOR C HEATHER ASHTON, DM, FRCP

Chrystal Heather Ashton DM, FRCP is Emeritus Professor of Clinical Psycho-pharmacology at the University of Newcastle upon Tyne, England.

Professor Ashton is a graduate of the University of Oxford and obtained a First Class Honours Degree (BA) in Physiology in 1951. She qualified in Medicine (BM, BCh, MA) in 1954 and gained a postgraduate Doctor of Medicine (DM) in 1956. She qualified as MRCP (Member of the Royal College of Physicians, London) in 1958 and was elected FRCP (Fellow of the Royal College of Physicians, London) in 1975. She also became National Health Service Consultant in Clinical Psychopharmacology in 1975 and National Health Service Consultant in Psychiatry in 1994.

She has worked at the University of Newcastle upon Tyne as researcher (Lecturer, Senior Lecturer, Reader and Professor) and clinician since 1965, first in the Department of Pharmacology and latterly in the Department of Psychiatry. Her research has centred, and continues, on the effects of psychotropic drugs (nicotine, cannabis, benzodiazepines, antidepressants and others) on the brain and behaviour in man. Her main clinical work was in running a benzodiazepine withdrawal clinic for 12 years from 1982-1994.

She is at present involved with the North East Council for Addictions (NECA) of which she is former Vice-Chairman of the Executive Committee on which she still serves. She continues to give advice on benzodiazepine problems to counsellors and is patron of the Bristol & District Tranquilliser Project. She was generic expert in the UK benzodiazepine litigation in the 1980s and has been involved with the UK organisation Victims of Tranquillisers (VOT). She has submitted evidence about benzodiazepines to the House of Commons Health Select Committee.

She has published approximately 250 papers in professional journals, books and chapters in books on psychotropic drugs of which over 50 concern benzodiazepines. She has given evidence to various Government committees on tobacco smoking, cannabis and benzodiazepines and has given invited lectures on benzodiazepines in the UK, Australia, Sweden, Switzerland and other countries.

SUMMARY OF CONTENTS

This monograph contains information about the effects that benzodiazepines have on the brain and body and how these actions are exerted. Detailed suggestions on how to withdraw after long-term use and individual tapering schedules for different benzodiazepines are provided. Withdrawal symptoms, acute and protracted, are described along with an explanation of why they may occur and how to cope with them. The overall message is that most long-term benzodiazepine users who wish to can withdraw successfully and become happier and healthier as a result.

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CHAPTER I

THE BENZODIAZEPINES: WHAT THEY DO IN THE BODY

BACKGROUND

For twelve years (1982-1994) I ran a Benzodiazepine Withdrawal Clinic for people wanting to come off their tranquillisers and sleeping pills. Much of what I know about this subject was taught to me by those brave and long-suffering men and women. By listening to the histories of over 300 "patients" and by closely following their progress (week-by-week and sometimes day-by-day), I gradually learned what long-term benzodiazepine use and subsequent withdrawal entails.

Most of the people attending the clinic had been taking benzodiazepines prescribed by their doctors for many years, sometimes over 20 years. They wished to stop because they did not

feel well. They realised that the drugs, though effective when first prescribed, might not be actually making them feel ill. They had many symptoms, both physical and mental. Some were depressed and/or anxious; some had "irritable bowel", cardiac or neurological complaints. Many had undergone hospital investigations with full gastrointestinal, cardiological and neurological screens (nearly always with negative results). A number had been told (wrongly) that they had multiple sclerosis. Several had lost their jobs through recurrent illnesses.

The experiences of these patients have since been confirmed in many studies, by thousands of patients attending tranquilliser support groups in the UK and other parts of Europe, and by individuals vainly seeking help in the US. It is interesting that the patients themselves, and not the medical profession, were the first to realise that long-term use of benzodiazepines can cause problems.

ABOUT THIS CHAPTER

Some readers may decide to go directly to the chapter on benzodiazepine withdrawal (Chapter II). However, those who wish to understand withdrawal symptoms and techniques (and therefore to cope better with the withdrawal process) are advised to become acquainted first with what benzodiazepines do in the body, how they work, how the body adjusts to chronic use, and why withdrawal symptoms occur. These issues are discussed in this chapter.

THE BENZODIAZEPINES

Potency. A large number of benzodiazepines are available (Table 1). There are major differences in potency between different benzodiazepines, so that equivalent doses vary as much as 20-fold. For example, 0.5 milligrams (mg) of alprazolam (Xanax) is approximately equivalent to 10mg of diazepam (Valium). Thus a person on 6mg of alprazolam daily, a dose not uncommonly prescribed in the US, is taking the equivalent of about 120mg of diazepam, a very high dose. These differences in strength have not always been fully appreciated by doctors, and some would not agree with the equivalents given here. Nevertheless, people on potent benzodiazepines such as alprazolam, lorazepam (Ativan) or clonazepam (Klonopin) tend to be using relatively large doses. This difference in potency is important when switching from one benzodiazepine to another, for example changing to diazepam during the withdrawal, as described in the next chapter.

Speed of elimination. Benzodiazepines also differ markedly in the speed at which they are metabolised (in the liver) and eliminated from the body (in the urine) (Table 1). For example, the "half-life" (time taken for the blood concentration to fall to half its initial value after a single dose) for triazolam (Halcion) is only 2-5 hours, while the half-life of diazepam is 20-100 hours, and that of an active metabolite of diazepam (desmethyldiazepam) is 36-200 hours. This means that half the active products of diazepam are still in the bloodstream up to 200 hours after a single dose. Clearly, with repeated daily dosing accumulation occurs and high concentrations can build up in

the body (mainly in fatty tissues). As Table 1 shows, there is a considerable variation between individuals in the rate at which they metabolise benzodiazepines.

Table 1. BENZODIAZEPINES AND SIMILAR DRUGS[5]

Benzodiazepines[5]	**Half-life (hrs)[1] [active metabolite]**	**Market Aim[2]**	**Approximately Equivalent Oral dosages (mg)[3]**
Alprazolam (Xanax)	6-12	a	0.5
Bromazepam (Lexotan, Lexomil)	10-20	a	5-6
Chlordiazepoxide (Librium)	5-30 [36-200]	a	25
Clobazam (Frisium)	12-60	a,e	20
Clonazepam (Klonopin, Rivotril)	18-50	a,e	0.5
Clorazepate (Tranxene)	[36-200]	a	15
Diazepam (Valium)	20-100 [36-200]	a	10
Estazolam (ProSom)	10-24	h	1-2
Flunitrazepam (Rohypnol)	18-26 [36-200]	h	1
Flurazepam (Dalmane)	[40-250]	h	15-30
Halazepam (Paxipam)	[30-100]	a	20
Ketazolam (Anxon)	30-100 [36-200]	a	15-30
Loprazolam (Dormonoct)	6-12	h	1-2

Lorazepam (Ativan)	10-20	a	1
Lormetazepam (Noctamid)	10-12	h	1-2
Medazepam (Nobrium)	36-200	a	10
Nitrazepam (Mogadon)	15-38	h	10
Nordazepam (Nordaz, Calmday)	36-200	a	10
Oxazepam (Serax, Serenid, Serepax)	4-15	a	20
Prazepam (Centrax)	[36-200]	a	10-20
Quazepam (Doral)	25-100	h	20
Temazepam (Restoril, Normison, Euhypnos)	8-22	h	20
Triazolam (Halcion)	2	h	0.5
Non-benzodiazepines with similar effects[4,5]			
Zaleplon (Sonata)	2	h	20
Zolpidem (Ambien, Stilnoct)	2	h	20
Zopiclone (Zimovane, Imovane)	5-6	h	15
Eszopiclone (Lunesta)	6 (9 in elderly)	h	3

1. Half-life: time taken for blood concentration to fall to half its peak value after a single dose. Half-life of active metabolite shown in square brackets. This time may vary considerably between individuals.

2. Market aim: although all benzodiazepines have similar actions, they are usually marketed as anxiolytics (a), hypnotics (h) or anticonvulsants (e).

3. These equivalents do not agree with those used by some authors. They are firmly based on clinical experience but may vary between individuals.

4. These drugs are chemically different from benzodiazepines but have the same effects on the body and act by the same mechanisms.

5. All these drugs are recommended for short-term use only (2-4 weeks maximum).

Duration of effects. The speed of elimination of a benzodiazepine is obviously important in determining the duration of its effects. However, the duration of apparent action is usually considerably less than the half-life. With most benzodiazepines, noticeable effects usually wear off within a few hours. Nevertheless the drugs, as long as they are present, continue to exert subtle effects within the body. These effects may become apparent during continued use or may appear as withdrawal symptoms when dosage is reduced or the drug is stopped.

Therapeutic actions of benzodiazepines. Regardless of their potency, speed of elimination or duration of effects, the actions in the body are virtually the same for all benzodiazepines. This is true whether they are marketed as anxiolytics, hypnotics or anti-convulsants (Table 1). All benzodiazepines exert five major effects which are used therapeutically: anxiolytic, hypnotic, muscle relaxant, anticonvulsant and amnesic (impairment of memory) (Table 2).

Table 2. THERAPEUTIC ACTIONS OF BENZODIAZEPINES (IN SHORT-TERM USE)

Action	Clinical Use
Anxiolytic - relief of anxiety	- Anxiety and panic disorders, phobias
Hypnotic - promotion of sleep	- Insomnia
Myorelaxant - muscle relaxation	- Muscle spasms, spastic disorders
Anticonvulsant - stop fits, convulsions	- Fits due to drug poisoning, some forms of epilepsy
Amnesia - impair short-term memory	- Premedication for operations, sedation for minor surgical procedures

Other clinical uses, utilising combined effects:

- Alcohol detoxification
- Acute psychosis with hyperexcitability and aggressiveness

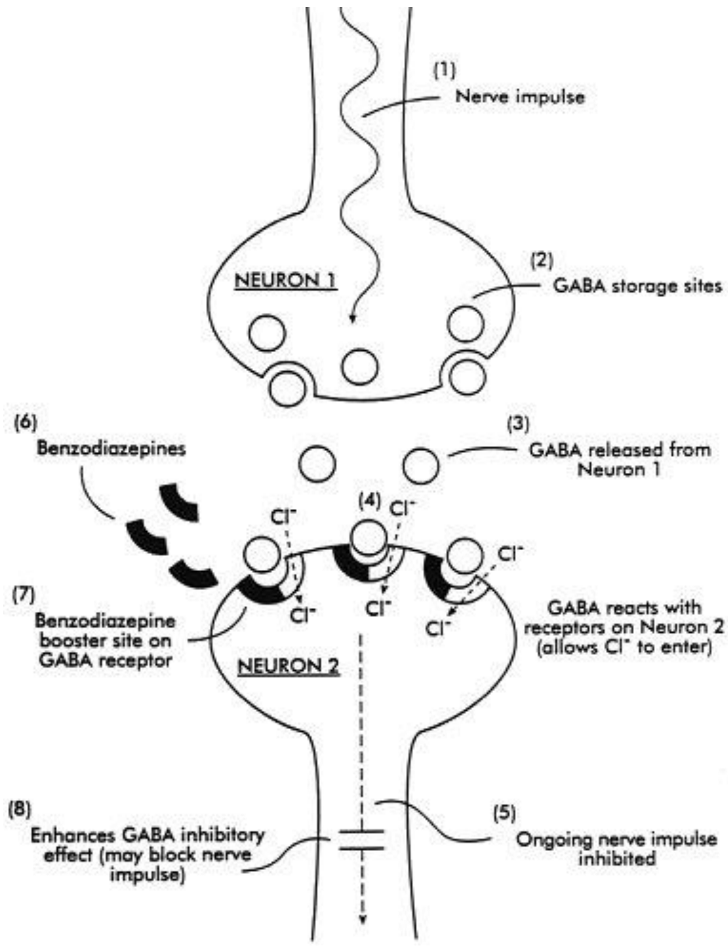
These actions, exerted by different benzodiazepines in slightly varying degrees, confer on the drugs some useful medicinal properties. Few drugs can compete with them in efficacy, rapid onset of action and low acute toxicity. In short-term use, benzodiazepines can be valuable,

sometimes even life-saving, across a wide range of clinical conditions as shown in Table 2. Nearly all the disadvantages of benzodiazepines result from long-term use (regular use for more than a few weeks). The UK Committee on Safety of Medicines in 1988 recommended that benzodiazepines should in general be reserved for short-term use (2-4 weeks only).

Mechanisms of action. Anyone struggling to get off their benzodiazepines will be aware that the drugs have profound effects on the mind and body apart from the therapeutic actions. Directly or indirectly, benzodiazepines in fact influence almost every aspect of brain function. For those interested to know how and why, a short explanation follows of the mechanisms through which benzodiazepines are able to exert such widespread effects.

All benzodiazepines act by enhancing the actions of a natural brain chemical, GABA (gamma-aminobutyric acid). GABA is a neurotransmitter, an agent which transmits messages from one brain cell (neuron) to another. The message that GABA transmits is an inhibitory one: it tells the neurons that it contacts to slow down or stop firing. Since about 40% of the millions of neurons all over the brain respond to GABA, this means that GABA has a general quietening influence on the brain: it is in some ways the body's natural hypnotic and tranquilliser. This natural action of GABA is augmented by benzodiazepines which thus exert an extra (often excessive) inhibitory influence on neurons (Fig. 1).

Fig. 1. Diagram of mechanism of action of the natural neurotransmitter GABA (gamma-aminobutyric acid) and benzodiazepines on nerve cells (neurons) in the brain



(1,2) Nerve impulse causes release of GABA from storage sites on neuron 1
(3) GABA released into space between neurons
(4) GABA reacts with receptors on neuron 2; the reaction allows chloride ions (Cl^-) to enter the neuron
(5) This effect inhibits further progress of the nerve impulse
(6,7) Benzodiazepines react with booster site on GABA receptors
(8) This action enhances the inhibitory effects of GABA; the ongoing nerve impulse may be completely blocked

The way in which GABA sends its inhibitory message is by a clever electronic device. Its reaction with special sites (GABA-receptors) on the outside of the receiving neuron opens a channel, allowing negatively charged particles (chloride ions) to pass to the inside of the neuron. These negative ions "supercharge" the neuron making it less responsive to other neurotransmitters which would normally excite it. Benzodiazepines also react at their own special sites (benzodiazepine receptors), situated actually on the GABA-receptor. Combination of a benzodiazepine at this site acts as a booster to the actions of GABA, allowing more chloride ions to enter the neuron, making it even more resistant to excitation. Various subtypes of benzodiazepine receptors have slightly different actions. One subtype (alpha 1) is responsible for sedative effects, another (alpha 2) for anti-anxiety effects, and both alpha 1 and alpha 2, as

well as alpha 5, for anticonvulsant effects. All benzodiazepines combine, to a greater or lesser extent, with all these subtypes and all enhance GABA activity in the brain.

As a consequence of the enhancement of GABA's inhibitory activity caused by benzodiazepines, the brain's output of excitatory neurotransmitters, including norepinephrine (noradrenaline), serotonin, acetyl choline and dopamine, is reduced. Such excitatory neurotransmitters are necessary for normal alertness, memory, muscle tone and co-ordination, emotional responses, endocrine gland secretions, heart rate and blood pressure control and a host of other functions, all of which may be impaired by benzodiazepines. Other benzodiazepine receptors, not linked to GABA, are present in the kidney, colon, blood cells and adrenal cortex and these may also be affected by some benzodiazepines. These direct and indirect actions are responsible for the well-known adverse effects of dosage with benzodiazepines.

ADVERSE EFFECTS OF BENZODIAZEPINES

Oversedation. Oversedation is a dose-related extension of the sedative/hypnotic effects of benzodiazepines. Symptoms include drowsiness, poor concentration, incoordination, muscle weakness, dizziness and mental confusion. When benzodiazepines are taken at night as sleeping pills, sedation may persist the next day as "hangover" effects, particularly with slowly eliminated preparations (Table 1). However, tolerance to the sedative effects usually develops over a week or two and anxious patients taking benzodiazepines during the day rarely complain of sleepiness although fine judgement and some memory functions may still be impaired.

Oversedation persists longer and is more marked in the elderly and may contribute to falls and fractures. Acute confusional states have occurred in the elderly even after small doses of benzodiazepines. Oversedation from benzodiazepines contributes to accidents at home and at work and studies from many countries have shown a significant association between the use of benzodiazepines and the risk of serious traffic accidents. People taking benzodiazepines should be warned of the risks of driving and of operating machinery.

Drug interactions. Benzodiazepines have additive effects with other drugs with sedative actions including other hypnotics, some antidepressants (e.g. amitriptyline [Elavil], doxepin [Adapin, Sinequan]), major tranquillisers or neuroleptics (e.g. prochlorperazine [Compazine], trifluoperazine [Stelazine]), anticonvulsants (e.g. phenobarbital, phenytoin [Dilantin], carbamazepine [Atretol, Tegretol]), sedative antihistamines (e.g. diphenhydramine [Benadryl], promethazine [Phenergan]), opiates (heroin, morphine, meperidine), and, importantly, alcohol. Patients taking benzodiazepines should be warned of these interactions. If sedative drugs are taken in overdose, benzodiazepines may add to the risk of fatality.

Memory impairment. Benzodiazepines have long been known to cause amnesia, an effect which is utilised when the drugs are used as premedication before major surgery or for minor surgical procedures. Loss of memory for unpleasant events is a welcome effect in these

circumstances. For this purpose, fairly large single doses are employed and a short-acting benzodiazepine (e.g. midazolam) may be given intravenously.

Oral doses of benzodiazepines in the dosage range used for insomnia or anxiety can also cause memory impairment. Acquisition of new information is deficient, partly because of lack of concentration and attention. In addition, the drugs cause a specific deficit in "episodic" memory, the remembering of recent events, the circumstances in which they occurred, and their sequence in time. By contrast, other memory functions (memory for words, ability to remember a telephone number for a few seconds, and recall of long-term memories) are not impaired. Impairment of episodic memory may occasionally lead to memory lapses or "blackouts". It is claimed that in some instances such memory lapses may be responsible for uncharacteristic behaviours such as shop-lifting.

Benzodiazepines are often prescribed for acute stress-related reactions. At the time they may afford relief from the distress of catastrophic disasters, but if used for more than a few days they may prevent the normal psychological adjustment to such trauma. In the case of loss or bereavement they may inhibit the grieving process which may remain unresolved for many years. In other anxiety states, including panic disorder and agoraphobia, benzodiazepines may inhibit the learning of alternative stress-coping strategies, including cognitive behavioural treatment.

Paradoxical stimulant effects. Benzodiazepines occasionally cause paradoxical excitement with increased anxiety, insomnia, nightmares, hallucinations at the onset of sleep, irritability, hyperactive or aggressive behaviour, and exacerbation of seizures in epileptics. Attacks of rage and violent behaviour, including assault (and even homicide), have been reported, particularly after intravenous administration but also after oral administration. Less dramatic increases in irritability and argumentativeness are much more common and are frequently remarked upon by patients or by their families. Such reactions are similar to those sometimes provoked by alcohol. They are most frequent in anxious and aggressive individuals, children, and the elderly. They may be due to release or inhibition of behavioural tendencies normally suppressed by social restraints. Cases of "baby-battering", wife-beating and "grandma-bashing" have been attributed to benzodiazepines.

Depression, emotional blunting. Long-term benzodiazepine users, like alcoholics and barbiturate-dependent patients, are often depressed, and the depression may first appear during prolonged benzodiazepine use. Benzodiazepines may both cause and aggravate depression, possibly by reducing the brain's output of neurotransmitters such as serotonin and norepinephrine (noradrenaline). However, anxiety and depression often co-exist and benzodiazepines are frequently prescribed for mixed anxiety and depression. Sometimes the drugs seem to precipitate suicidal tendencies in such patients. Of the first 50 of the patients attending my withdrawal clinic (reported in 1987), ten had taken drug overdoses requiring hospital admission while on chronic benzodiazepine medication; only two of these had a history of depressive illness before they were prescribed benzodiazepines. The depression lifted in

these patients after benzodiazepine withdrawal and none took further overdoses during the 10 months to 3.5 years follow-up period after withdrawal. In 1988 the Committee on Safety of Medicines in the UK recommended that "benzodiazepines should not be used alone to treat depression or anxiety associated with depression. Suicide may be precipitated in such patients".

"Emotional anaesthesia", the inability to feel pleasure or pain, is a common complaint of long-term benzodiazepine users. Such emotional blunting is probably related to the inhibitory effect of benzodiazepines on activity in emotional centres in the brain. Former long-term benzodiazepine users often bitterly regret their lack of emotional responses to family members - children and spouses or partners - during the period when they were taking the drugs. Chronic benzodiazepine use can be a cause of domestic disharmony and even marriage break-up.

Adverse effects in the elderly. Older people are more sensitive than younger people to the central nervous system depressant effects of benzodiazepines. Benzodiazepines can cause confusion, night wandering, amnesia, ataxia (loss of balance), hangover effects and "pseudodementia" (sometimes wrongly attributed to Alzheimer's disease) in the elderly and should be avoided wherever possible. Increased sensitivity to benzodiazepines in older people is partly because they metabolise drugs less efficiently than younger people, so that drug effects last longer and drug accumulation readily occurs with regular use. However, even at the same blood concentration, the depressant effects of benzodiazepines are greater in the elderly, possibly because they have fewer brain cells and less reserve brain capacity than younger people.

For these reasons, it is generally advised that, if benzodiazepines are used in the elderly, dosage should be half that recommended for adults, and use (as for adults) should be short-term (2 weeks) only. In addition, benzodiazepines without active metabolites (e.g. oxazepam [Serax], temazepam [Restoril]) are tolerated better than those with slowly eliminated metabolites (e.g. chlordiazepoxide [Librium], nitrazepam [Mogadon]). Equivalent potencies of different benzodiazepines are approximately the same in older as in younger people (Table 1).

Adverse effects in pregnancy. Benzodiazepines cross the placenta, and if taken regularly by the mother in late pregnancy, even in therapeutic doses, can cause neonatal complications. The foetus and neonate metabolise benzodiazepines very slowly, and appreciable concentrations may persist in the infant up to two weeks after birth, resulting in the "floppy infant syndrome" of lax muscles, oversedation, and failure to suckle. Withdrawal symptoms may develop after about two weeks with hyperexcitability, high-pitched crying and feeding difficulties.

Benzodiazepines in therapeutic doses appear to carry little risk of causing major congenital malformations. However, chronic maternal use may impair foetal intrauterine growth and retard brain development. There is increasing concern that such children in later life may be prone to attention deficit disorder, hyperactivity, learning difficulties, and a spectrum of autistic disorders.

Tolerance. Tolerance to many of the effects of benzodiazepines develops with regular use: the original dose of the drug has progressively less effect and a higher dose is required to obtain the original effect. This has often led doctors to increase the dosage in their prescriptions or to add another benzodiazepine so that some patients have ended up taking two benzodiazepines at once.

However, tolerance to the various actions of benzodiazepines develops at variable rates and to different degrees. Tolerance to the hypnotic effects develops rapidly and sleep recordings have shown that sleep patterns, including deep sleep (slow wave sleep) and dreaming (which are initially suppressed by benzodiazepines), return to pre-treatment levels after a few weeks of regular benzodiazepine use. Similarly, daytime users of the drugs for anxiety no longer feel sleepy after a few days.

Tolerance to the anxiolytic effects develops more slowly but there is little evidence that benzodiazepines retain their effectiveness after a few months. In fact long-term benzodiazepine use may even aggravate anxiety disorders. Many patients find that anxiety symptoms gradually increase over the years despite continuous benzodiazepine use, and panic attacks and agoraphobia may appear for the first time after years of chronic use. Such worsening of symptoms during long-term benzodiazepine use is probably due to the development of tolerance to the anxiolytic effects, so that "withdrawal" symptoms emerge even in the continued presence of the drugs. However, tolerance may not be complete and chronic users sometimes report continued efficacy, which may be partly due to suppression of withdrawal effects. Nevertheless, in most cases such symptoms gradually disappear after successful tapering and withdrawal of benzodiazepines. Among the first 50 patients attending my clinic, 10 patients became agoraphobic for the first time while taking benzodiazepines. Agoraphobic symptoms abated dramatically within a year of withdrawal, even in patients who had been housebound, and none were incapacitated by agoraphobia at the time of follow-up (10 months to 3.5 years after withdrawal).

Tolerance to the anticonvulsant effects of benzodiazepines makes them generally unsuitable for long-term control of epilepsy. Tolerance to the motor effects of benzodiazepines can develop to a remarkable degree so that people on very large doses may be able to ride a bicycle and play ball games. However, complete tolerance to the effects on memory and cognition does not seem to occur. Many studies show that these functions remain impaired in chronic users, recovering slowly, though sometimes incompletely, after withdrawal.

Tolerance is a phenomenon that develops with many chronically used drugs (including alcohol, heroin and morphine and cannabis). The body responds to the continued presence of the drug with a series of adjustments that tend to overcome the drug effects. In the case of benzodiazepines, compensatory changes occur in the GABA and benzodiazepine receptors which become less responsive, so that the inhibitory actions of GABA and benzodiazepines are decreased. At the same time there are changes in the secondary systems controlled by GABA so that the activity of excitatory neurotransmitters tends to be restored. Tolerance to different

effects of benzodiazepines may vary between individuals - probably as a result of differences in intrinsic neurological and chemical make-up which are reflected in personality characteristics and susceptibility to stress. The development of tolerance is one of the reasons people become dependent on benzodiazepines, and also sets the scene for the withdrawal syndrome, described in the next chapter.

Dependence. Benzodiazepines are potentially addictive drugs: psychological and physical dependence can develop within a few weeks or months of regular or repeated use. There are several overlapping types of benzodiazepine dependence.

Therapeutic dose dependence. People who have become dependent on therapeutic doses of benzodiazepines usually have several of the following characteristics.

1. They have taken benzodiazepines in prescribed "therapeutic" (usually low) doses for months or years.
2. They have gradually become to "need" benzodiazepines to carry out normal, day-to-day activities.
3. They have continued to take benzodiazepines although the original indication for prescription has disappeared.
4. They have difficulty in stopping the drug, or reducing dosage, because of withdrawal symptoms.
5. If on short-acting benzodiazepines (Table 1) they develop anxiety symptoms between doses, or get craving for the next dose.
6. They contact their doctor regularly to obtain repeat prescriptions.
7. They become anxious if the next prescription is not readily available; they may carry their tablets around with them and may take an extra dose before an anticipated stressful event or a night in a strange bed.
8. They may have increased the dosage since the original prescription.
9. They may have anxiety symptoms, panics, agoraphobia, insomnia, depression and increasing physical symptoms despite continuing to take benzodiazepines.

The number of people world-wide who are taking prescribed benzodiazepines is enormous. For example, in the US nearly 11 per cent of a large population surveyed in 1990 reported some benzodiazepine use the previous year. About 2 per cent of the adult population of the US (around 4 million people) appear to have used prescribed benzodiazepine hypnotics or tranquillisers regularly for 5 to 10 years or more. Similar figures apply in the UK, over most of

Europe and in some Asian countries. A high proportion of these long-term users must be, at least to some degree, dependent. Exactly how many are dependent is not clear; it depends to some extent on how dependence is defined. However, many studies have shown that 50-100 per cent of long-term users have difficulty in stopping benzodiazepines because of withdrawal symptoms, which are described in Chapter III.

Prescribed high dose dependence. A minority of patients who start on prescribed benzodiazepines begin to "require" larger and larger doses. At first they may persuade their doctors to escalate the size of prescriptions, but on reaching the prescriber's limits, may contact several doctors or hospital departments to obtain further supplies which they self-prescribe. Sometimes this group combines benzodiazepine misuse with excessive alcohol consumption. Patients in this group tend to be highly anxious, depressed and may have personality difficulties. They may have a history of other sedative or alcohol misuse. They do not typically use illicit drugs but may obtain "street" benzodiazepines if other sources fail.

Recreational benzodiazepine abuse. Recreational use of benzodiazepines is a growing problem. A large proportion (30-90 per cent) of polydrug abusers world-wide also use benzodiazepines. Benzodiazepines are used in this context to increase the "kick" obtained from illicit drugs, particularly opiates, and to alleviate the withdrawal symptoms of other drugs of abuse (opiates, barbiturates, cocaine, amphetamines and alcohol). People who have been given benzodiazepines during alcohol detoxification sometimes become dependent on benzodiazepines and may abuse illicitly obtained benzodiazepines as well as relapsing into alcohol use. Occasionally high doses of benzodiazepines are used alone to obtain a "high". Recreational use of diazepam, alprazolam, lorazepam, temazepam, triazolam, flunitrazepam and others has been reported in various countries. Usually the drugs are taken orally, often in doses much greater than those used therapeutically (e.g.100mg diazepam or equivalent daily) but some users inject benzodiazepines intravenously. These high dose users develop a high degree of tolerance to benzodiazepines and, although they may use the drugs intermittently, some become dependent. Detoxification of these patients may present difficulties since withdrawal reactions can be severe and include convulsions.

The present population of recreational users may be relatively small, perhaps one tenth of that of long-term prescribed therapeutic dose users, but probably amounts to some hundreds of thousands in the US and Western Europe, and appears to be increasing. It is a chastening thought that medical overprescription of benzodiazepines, resulting in their presence in many households, made them easily available and undoubtedly aided their entry into the illicit drug scene. Present sources for illicit users are forged prescriptions, theft from drug stores, or illegal imports.

Socioeconomic costs of long-term benzodiazepine use. The socio-economic costs of the present high level of long-term benzodiazepine use are considerable, although difficult to quantify. Most of these have been mentioned above and are summarised in Table 3. These consequences could be minimised if prescriptions for long-term benzodiazepines were

decreased. Yet many doctors continue to prescribe benzodiazepines and patients wishing to withdraw receive little advice or support on how to go about it. The following chapter gives practical information on withdrawal which, it is hoped, will be of use both to long-term benzodiazepine users and to their physicians.

TABLE 3. SOME SOCIOECONOMIC COSTS OF LONG-TERM BENZODIAZEPINE USE

1. Increased risk of accidents - traffic, home, work.
2. Increased risk of fatality from overdose if combined with other drugs.
3. Increased risk of attempted suicide, especially in depression.
4. Increased risk of aggressive behaviour and assault.
5. Increased risk of shoplifting and other antisocial acts.
6. Contributions to marital/domestic disharmony and breakdown due to emotional and cognitive impairment.
7. Contributions to job loss, unemployment, loss of work through illness.
8. Cost of hospital investigations/consultations/admissions.
9. Adverse effects in pregnancy and in the new-born.
10. Dependence and abuse potential (therapeutic and recreational).
11. Costs of drug prescriptions.
12. Costs of litigation.

FURTHER READING

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CHAPTER II

HOW TO WITHDRAW FROM BENZODIAZEPINES AFTER LONG-TERM USE

BACKGROUND

At the start of my Benzodiazepine Withdrawal Clinic in 1982, no-one had much experience in benzodiazepine withdrawal. Yet, as explained in Chapter I, there was strong pressure from the patients themselves for help and advice on how to withdraw. So, together, we felt our way. At first the withdrawal was a process of mutual trial (and sometimes error), but through this experience some general principles of withdrawal - what works best for most people - emerged. These general principles, derived from the 300 who attended the clinic up till 1994, have been confirmed over succeeding years by hundreds more benzodiazepine users with whom I have been involved through tranquilliser support groups in the UK and abroad and by personal contacts with individuals in many countries.

It soon became clear that each person's experience of withdrawal is unique. Although there are many features in common, every individual has his/her own personal pattern of withdrawal symptoms. These differ in type, quality, severity, time-course, duration, and many other features. Such variety is not surprising since the course of withdrawal depends on many factors: the dose, type, potency, duration of action and length of use of a particular benzodiazepine, the reason it was prescribed, the personality and individual vulnerability of the patient, his or her lifestyle, personal stresses and past experiences, the rate of withdrawal, and the degree of support available during and after withdrawal, to name but a few. For this reason the advice about withdrawal which follows is only a general guide; each individual must seek out the details of his own pathway. But the guide is gleaned from the successful withdrawal experiences of a

large number of men and women aged 18-80 with different home backgrounds, occupations, drug histories and rates of withdrawal. The success rate has been high (over 90%), and those who have withdrawn, even after taking benzodiazepines for over 20 years, have felt better both physically and mentally.

So, for those starting out, many previous users will testify that almost anyone who really wants to can withdraw from benzodiazepines. But don't be surprised if your symptoms (or lack of them) are different from those of anyone else embarking on the same venture.

WHY SHOULD YOU COME OFF BENZODIAZEPINES?

As described in Chapter I, long-term use of benzodiazepines can give rise to many unwanted effects, including poor memory and cognition, emotional blunting, depression, increasing anxiety, physical symptoms and dependence. All benzodiazepines can produce these effects whether taken as sleeping pills or anti-anxiety drugs. The social and economic consequences of chronic benzodiazepine use are summarised in Table 3 (Chapter I).

Furthermore, the evidence suggests that benzodiazepines are no longer effective after a few weeks or months of regular use. They lose much of their efficacy because of the development of tolerance. When tolerance develops, "withdrawal" symptoms can appear even though the user continues to take the drug. Thus the symptoms suffered by many long-term users are a mixture of adverse effects of the drugs and "withdrawal" effects due to tolerance. The Committee on Safety of Medicines and the Royal College of Psychiatrists in the UK concluded in various statements (1988 and 1992) that benzodiazepines are unsuitable for long-term use and that they should in general be prescribed for periods of 2-4 weeks only.

In addition, clinical experience shows that most long-term benzodiazepine users actually feel better after coming off the drugs. Many users have remarked that it was not until they came off their drugs that they realised they had been operating below par for all the years they had been taking them. It was as though a net curtain or veil had been lifted from their eyes: slowly, sometimes suddenly, colours became brighter, grass greener, mind clearer, fears vanished, mood lifted, and physical vigour returned.

Thus there are good reasons for long-term users to stop their benzodiazepines if they feel unhappy about the medication. Many people are frightened of withdrawal, but reports of having to "go through hell" can be greatly exaggerated. With a sufficiently gradual and individualised tapering schedule, as outlined below, withdrawal can be quite tolerable, even easy, especially when the user understands the cause and nature of any symptoms that do arise and is therefore not afraid. Many "withdrawal symptoms" are simply due to fear of withdrawal (or even fear of that fear). People who have had bad experiences have usually been withdrawn too quickly (often by doctors!) and without any explanation of the symptoms. At the other extreme, some people can stop their benzodiazepines with no symptoms at all: according to some

authorities, this figure may be as high as 50% even after a year of chronic usage. Even if this figure is correct (which is arguable) it is unwise to stop benzodiazepines suddenly.

The advantages of discontinuing benzodiazepines do not necessarily mean that every long-term user should withdraw. Nobody should be forced or persuaded to withdraw against his or her will. In fact, people who are unwillingly pushed into withdrawal often do badly. On the other hand, the chances of success are very high for those sufficiently motivated. As mentioned before, almost anyone who really wants to come off can come off benzodiazepines. The option is up to you.

BEFORE STARTING BENZODIAZEPINE WITHDRAWAL

Once you have made up your mind to withdraw, there are some steps to take before you start.

(1) Consult your doctor and pharmacist. Your doctor may have views on whether it is appropriate for you to stop your benzodiazepines. In a small number of cases withdrawal may be inadvisable. Some doctors, particularly in the US, believe that long-term benzodiazepines are indicated for some anxiety, panic and phobic disorders and some psychiatric conditions. However, medical opinions differ and, even if complete withdrawal is not advised, it may be beneficial to reduce the dosage or to take intermittent courses with benzodiazepine-free intervals.

Your doctor's agreement and co-operation is necessary since he/she will be prescribing the medication. Many doctors are uncertain how to manage benzodiazepine withdrawal and hesitate to undertake it. But you can reassure your doctor that you intend to be in charge of your own program and will proceed at whatever pace you find comfortable, although you may value his advice from time to time. It is important for **you** to be in control of your own schedule. Do not let your doctor impose a deadline. Leave yourself free to "proceed as the way openeth", as the Quakers say.

It is a good idea to make out a dosage reduction schedule for the initial stages (see below) and to give your doctor a copy. You may need to mention the importance of flexibility, so that the rate of dosage tapering can be amended at any time. There may even be circumstances when you need to stop for a while at a certain stage. A continuation schedule can follow later depending upon how you get on, and the doctor can continue prescribing in accordance with the new schedule. (All this is explained later in this chapter).

Finally, your doctor may appreciate receiving some literature on benzodiazepine withdrawal, for example the articles mentioned under Further Reading at the end of Chapters I & III and of this chapter.

(2) Make sure you have adequate psychological support. Support could come from your spouse, partner, family or close friend. An understanding doctor may also be the one to offer support as well as advice. Ideally, your mentor should be someone who understands about

benzodiazepine withdrawal or is prepared to read about it and learn. It need not be someone who has gone through withdrawal - sometimes ex-users who have had a bad experience can frighten others by dwelling on their own symptoms. Often the help of a clinical psychologist, trained counsellor, or other therapist is valuable, especially for teaching relaxation techniques, deep breathing, how to deal with a panic attack etc. Some people find alternative techniques such as aromatherapy, acupuncture or yoga helpful, but these probably act only as an aid to relaxation. In my experience, hypnotherapy has not been helpful in long-term benzodiazepine users. Relaxation techniques are described in Chapter III.

Rather than (or in addition to) expensive therapists, you need someone reliable, who will support you frequently and regularly, long-term, both during withdrawal and for some months afterwards. Voluntary tranquilliser support groups (self-help groups) can be extremely helpful. They are usually run by people who have been through withdrawal and therefore understand the time and patience required, and can provide information about benzodiazepines. It can be encouraging to find that you are not alone, that there are plenty of others with similar problems to yours. However, do not be misled into fearing that you will get all the symptoms described by the others. Everyone is different and some people, with the right schedule and the right support, get no untoward symptoms at all. Many people in fact have managed to come off on their own without any outside help.

(3) Get into the right frame of mind.

- **Be confident** - you **can** do it. If in doubt, try a very small reduction in dosage for a few days (for example, try reducing your daily dosage by about one tenth or one eighth; you may be able to achieve this by halving or quartering one of your tablets). You will probably find that you notice no difference. If still in doubt, aim at first for dosage reduction rather than complete withdrawal. You will probably wish to continue once you have started.

- **Be patient.** There is no need to hurry withdrawal. Your body (and brain) may need time to readjust after years of being on benzodiazepines. Many people have taken a year or more to complete the withdrawal. So don't rush, and, above all, do not try to stop suddenly.

- **Choose your own way** - don't expect a "quick fix". It may be possible to enter a hospital or special centre for "detoxification". Such an approach usually involves a fairly rapid withdrawal, is medically "safe" and may provide psychological support. Such centres may be suitable for a small minority of people with difficult psychological problems. However, they often remove the control of withdrawal from the patient and setbacks on returning home are common, largely because there has been no time to build up alternative living skills. Slow withdrawal in your own environment allows time for physical and psychological adjustments, permits you to continue with your normal life, to tailor your withdrawal to your own lifestyle, and to build up alternative strategies for living without benzodiazepines.

THE WITHDRAWAL

(1) Dosage tapering. There is absolutely no doubt that anyone withdrawing from long-term benzodiazepines must reduce the dosage slowly. Abrupt or over-rapid withdrawal, especially from high dosage, can give rise to severe symptoms (convulsions, psychotic reactions, acute anxiety states) and may increase the risk of protracted withdrawal symptoms (see Chapter III). Slow withdrawal means tapering dosage gradually, usually over a period of some months. The aim is to obtain a smooth, steady and slow decline in blood and tissue concentrations of benzodiazepines so that the natural systems in the brain can recover their normal state. As explained in Chapter I, long-term benzodiazepines take over many of the functions of the body's natural tranquilliser system, mediated by the neurotransmitter GABA. As a result, GABA receptors in the brain reduce in numbers and GABA function decreases. Sudden withdrawal from benzodiazepines leaves the brain in a state of GABA-underactivity, resulting in hyperexcitability of the nervous system. This hyperexcitability is the root cause of most of the withdrawal symptoms discussed in the next chapter. However, a sufficiently slow, and smooth, departure of benzodiazepines from the body permits the natural systems to regain control of the functions which have been damped down by their presence. There is scientific evidence that reinstatement of brain function takes a long time. Recovery after long-term benzodiazepine use is not unlike the gradual recuperation of the body after a major surgical operation. Healing, of body or mind, is a slow process.

The precise rate of withdrawal is an individual matter. It depends on many factors including the dose and type of benzodiazepine used, duration of use, personality, lifestyle, previous experience, specific vulnerabilities, and the (perhaps genetically determined) speed of your recovery systems. Usually the best judge is you, yourself; you must be in control and must proceed at the pace that is comfortable for you. You may need to resist attempts from outsiders (clinics, doctors) to persuade you into a rapid withdrawal. The classic six weeks withdrawal period adopted by many clinics and doctors is much too fast for many long-term users. Actually, the rate of withdrawal, as long as it is slow enough, is not critical. Whether it takes 6 months, 12 months or 18 months is of little significance if you have taken benzodiazepines for a matter of years.

It is sometimes claimed that very slow withdrawal from benzodiazepines "merely prolongs the agony" and it is better to get it over with as quickly as possible. However, the experience of most patients is that slow withdrawal is greatly preferable, especially when the subject dictates the pace. Indeed, many patients find that there is little or no "agony" involved. Nevertheless there is no magic rate of withdrawal and each person must find the pace that suits him best. People who have been on low doses of benzodiazepine for a relatively short time (less than a year) can usually withdraw fairly rapidly. Those who have been on high doses of potent benzodiazepines such as Xanax and Klonopin are likely to need more time.

Examples of slow withdrawal schedules are given at the end of this chapter. As a very rough guide, a person taking 40mg diazepam a day (or its equivalent) might be able to reduce the

daily dosage by 2mg every 1-2 weeks until a dose of 20mg diazepam a day is reached. This would take 10-20 weeks. From 20mg diazepam a day, reductions of 1 mg in daily dosage every week or two might be preferable. This would take a further 20-40 weeks, so the total withdrawal might last 30-60 weeks. Yet some people might prefer to reduce faster and some might go even slower. (See next section for further details).

However, it is important in withdrawal always to go forwards. If you reach a difficult point, you can stop there for a few weeks if necessary, but you should try to avoid going backwards and increasing your dosage again. Some doctors advocate the use of "escape pills" (an extra dose of benzodiazepines) in particularly stressful situations. This is probably not a good idea as it interrupts the smooth decline in benzodiazepine concentrations and also disrupts the process of learning to cope without drugs which is an essential part of the adaptation to withdrawal. If the withdrawal is slow enough, "escape pills" should not be necessary.

(2) Switching to a long-acting benzodiazepine. With relatively short-acting benzodiazepines such as alprazolam (Xanax) and lorazepam (Ativan) (Table 1, Chapter I), it is not possible to achieve a smooth decline in blood and tissue concentrations. These drugs are eliminated fairly rapidly with the result that concentrations fluctuate with peaks and troughs between each dose. It is necessary to take the tablets several times a day and many people experience a "mini-withdrawal", sometimes a craving, between each dose.

For people withdrawing from these potent, short-acting drugs it is advisable to switch to a long-acting, slowly metabolised benzodiazepine such as diazepam. Diazepam (Valium) is one of the most slowly eliminated benzodiazepines. It has a half-life of up to 200 hours, which means that the blood level for each dose falls by only half in about 8.3 days. The only other benzodiazepines with similar half-lives are chlordiazepoxide (Librium), flunitrazepam (Rohypnol) and flurazepam (Dalmane), all of which are converted to a diazepam metabolite in the body. The slow elimination of diazepam allows a smooth, gradual fall in blood level, allowing the body to adjust slowly to a decreasing concentration of the benzodiazepines. The switch-over process needs to be carried out gradually, usually in stepwise fashion, substituting one dose at a time. There are several factors to consider. One is the difference in potency between different benzodiazepines. Many people have suffered because they have been switched suddenly to a different, less potent drug in inadequate dosage because the doctor has not adequately considered this factor. Equivalent potencies of benzodiazepines are shown in Table 1 (Chapter I), but these are only approximate and differ between individuals.

A second factor to bear in mind is that the various benzodiazepines, though broadly similar, have slightly different profiles of action. For example, lorazepam (Ativan) seems to have less hypnotic activity than diazepam (probably because it is shorter acting). Thus if someone on, say, 2mg Ativan three times a day is directly switched to 60mg diazepam (the equivalent dose for anxiety) he is liable to become extremely sleepy, but if he is switched suddenly onto a much smaller dose of diazepam, he will probably get withdrawal symptoms. Making the changeover one dose (or part of dose) at a time avoids this difficulty and also helps to find the equivalent

dosage for that individual. It is also helpful to make the first substitution in the night-time dose, and the substitution may not always need to be complete. For example, if the evening dose was 2mg Ativan, this could in some cases be changed to 1 mg Ativan plus 8mg diazepam. A full substitution for the dropped 1 mg of Ativan would have been 10mg diazepam. However, the patient may actually sleep well on this combination and he will have already made a dosage reduction - a first step in withdrawal. (Examples of step-wise substitutions are given in the schedules at the end of this chapter.)

A third important practical factor is the available dosage formulations of the various benzodiazepines. In withdrawal you need a long-acting drug which can be reduced in very small steps. Diazepam (Valium) is the only benzodiazepine that is ideal for this purpose since it comes in 2mg tablets, which are scored down the middle and easily halved into 1 mg doses. By contrast, the smallest available tablet of lorazepam (Ativan) is 0.5mg (equivalent to 5mg diazepam) [in the UK the lowest available dosage form for lorazepam is 1mg]; the smallest tablet of alprazolam (Xanax) is 0.25mg (also equivalent to 5mg diazepam). Even by halving these tablets the smallest reduction one could easily make is the equivalent of 2.5mg diazepam. (Some patients become very adept at shaving small portions off their tablets). Because of limited dose formulations, it may be necessary to switch to diazepam even if you are on a fairly long-acting benzodiazepine of relatively low potency (e.g. flurazepam [Dalmane]). Liquid preparations of some benzodiazepines are available and if desired slow reduction from these can be accomplished by decreasing the volume of each dose, using a graduated syringe.

Some doctors in the US switch patients onto clonazepam (Klonopin, [Rivotril in Canada]), believing that it will be easier to withdraw from than say alprazolam (Xanax) or lorazepam (Ativan) because it is more slowly eliminated. However, Klonopin is far from ideal for this purpose. It is an extremely potent drug, is eliminated much faster than diazepam (See Table 1, Chapter I), and the smallest available tablet in the US is 0.5mg (equivalent to 10mg diazepam) and 0.25mg in Canada (equivalent to 5mg Valium). It is difficult with this drug to achieve a smooth, slow fall in blood concentration, and there is some evidence that withdrawal is particularly difficult from high potency benzodiazepines, including Klonopin. Some people, however, appear to have particular difficulty in switching from Klonopin to diazepam. In such cases it is possible to have special capsules made up containing small doses, e.g. an eighth or a sixteenth of a milligram or less, which can be used to make gradual dosage reductions straight from Klonopin. These capsules require a doctor's prescription and can be made up by hospital pharmacists and some chemists in the UK, and by compounding pharmacists in North America. A similar technique can be used for those on other benzodiazepines who find it hard to substitute diazepam. To locate a compounding pharmacist in the USA or Canada this web site may be useful: www.iacprx.org. Care must be taken to ensure that the compounding pharmacist can guarantee the same formula on each prescription renewal. It should be noted, however, that this approach to benzodiazepine withdrawal can be troublesome and is not recommended for general use.

(3) Designing and following the withdrawal schedule. Some examples of withdrawal schedules are given on later pages. Most of them are actual schedules which have been used and found to work by real people who withdrew successfully. But each schedule must be tailored to individual needs; no two schedules are necessarily the same. Below is a summary of points to consider when drawing up your own schedule.

1. Design the schedule around your own symptoms. For example, if insomnia is a major problem, take most of your dosage at bedtime; if getting out of the house in the morning is a difficulty, take some of the dose first thing (but not a large enough dose to make you sleepy or incompetent at driving!).

2. When switching over to diazepam, substitute one dose at a time, usually starting with the evening or night-time dose, then replace the other doses, one by one, at intervals of a few days or a week. Unless you are starting from very large doses, there is no need to aim for a reduction at this stage; simply aim for an approximately equivalent dosage. When you have done this, you can start reducing the diazepam slowly.

   If, however, you are on a high dose, such as 6mg alprazolam (equivalent to 120mg diazepam), you may need to undertake some reduction while switching over, and may need to switch only part of the dosage at a time (see Schedule 1). The aim is to find a dose of diazepam which largely prevents withdrawal symptoms but is not so excessive as to make you sleepy.

3. Diazepam is very slowly eliminated and needs only, at most, twice daily administration to achieve smooth blood concentrations. If you are taking benzodiazepines three or four times a day it is advisable to space out your dosage to twice daily once you are on diazepam. The less often you take tablets the less your day will revolve around your medication.

4. The larger the dose you are taking initially, the greater the size of each dose reduction can be. You could aim at reducing dosage by up to one tenth at each decrement. For example, if you are taking 40mg diazepam equivalent you could reduce at first by 2-4mg every week or two. When you are down to 20mg, reductions could be 1-2mg weekly or fortnightly. When you are down to 10mg, 1mg reductions are probably indicated. From 5mg diazepam some people prefer to reduce by 0.5mg every week or two.

5. There is no need to draw up your withdrawal schedule right up to the end. It is usually sensible to plan the first few weeks and then review and if necessary amend your schedule according to your progress. Prepare your doctor to be flexible and to be ready for your schedule to be adjusted to a slower (or faster) pace at any time.

6. As far as possible, never go backwards. You can stand still at a certain stage in your schedule and have a vacation from further withdrawal for a few weeks if circumstances change (if for instance there is a family crisis), but try to avoid ever increasing the dosage again. You don't want to back over ground you have already covered.

7. Avoid taking extra tablets in times of stress. Learn to gain control over your symptoms. This will give you extra confidence that you can cope without benzodiazepines (see Chapter III, Withdrawal Symptoms).

8. Avoid compensating for benzodiazepines by increasing your intake of alcohol, cannabis or non-prescription drugs. Occasionally your doctor may suggest other drugs for particular symptoms (see Chapter III, Withdrawal Symptoms), but do not take the sleeping tablets zolpidem (Ambien), zopiclone (Zimovane, Imovane) or zaleplon (Sonata) as they have the same actions as benzodiazepines.

9. Getting off the last tablet: Stopping the last few milligrams is often viewed as particularly difficult. This is mainly due to fear of how you will cope without any drug at all. In fact, the final parting is surprisingly easy. People are usually delighted by the new sense of freedom gained. In any case the 1mg or 0.5mg diazepam per day which you are taking at the end of your schedule is having little effect apart from keeping the dependence going. Do not be tempted to spin out the withdrawal to a ridiculously slow rate towards the end (such as 0.25mg each month). Take the plunge when you reach 0.5mg daily; full recovery cannot begin until you have got off your tablets completely. Some people after completing withdrawal like to carry around a few tablets with them for security "just in case", but find that they rarely if ever use them.

10. Do not become obsessed with your withdrawal schedule. Let it just become a normal way of life for the next few months. Okay, you are withdrawing from your benzodiazepines; so are many others. It's no big deal.

11. If for any reason you do not (or did not) succeed at your first attempt at benzodiazepine withdrawal, you can always try again. They say that most smokers make 7 or 8 attempts before they finally give up cigarettes. The good news is that most long-term benzodiazepine users are successful after the first attempt. Those who need a second try have usually been withdrawn too quickly the first time. A slow and steady benzodiazepine withdrawal, with you in control, is nearly always successful.

(4) Withdrawal in older people. Older people can withdraw from benzodiazepines as successfully as younger people, even if they have taken the drugs for years. A recent trial with an elderly population of 273 general practice patients on long-term (mean 15 years) benzodiazepines showed that voluntary dosage reduction and total withdrawal of benzodiazepines was accompanied by better sleep, improvement in psychological and physical

health and fewer visits to doctors. These findings have been repeated in several other studies of elderly patients taking benzodiazepines long-term.

There are particularly compelling reasons why older people should withdraw from benzodiazepines since, as age advances, they become more prone to falls and fractures, confusion, memory loss and psychiatric problems (see Chapter 1).

Methods of benzodiazepine withdrawal in older people are similar to those recommended above for younger adults. A slow tapering regimen, in my experience, is easily tolerated, even by people in their 80s who have taken benzodiazepines for 20 or more years. The schedule may include the use of liquid preparations if available and judicious stepwise substitution with diazepam (Valium) if necessary. There is, of course, a great deal of variation in the age at which individuals become "older" - perhaps 65-70 years would fit the definition in most cases.

(5) Antidepressants. Many people taking benzodiazepines long-term have also been prescribed antidepressant drugs because of developing depression, either during chronic use or during withdrawal. Antidepressant drugs should also be tapered slowly since they too can cause a withdrawal reaction (euphemistically labelled "antidepressant discontinuation reaction" by psychiatrists). If you are taking an antidepressant drug as well as a benzodiazepine it is best to complete the benzodiazepine withdrawal before starting to taper the antidepressant. A list of antidepressant drugs and brief advice on how to taper them is given in Schedule 13 of this chapter. Some antidepressant withdrawal ("discontinuation") symptoms are shown in Chapter III (Table 2).

The above summary applies to people who are planning to manage their own withdrawal - probably the majority of readers. Those who have the help of a knowledgeable and understanding doctor or counsellor may wish to share the burden somewhat. In my withdrawal clinic I used usually to draw up a draft schedule which I discussed with each patient. Most patients took a close interest in the schedule and suggested amendments from time to time. However, there were some who preferred not to think about the details too much but simply to follow the schedule rigidly to the end. This group was equally successful. A very few (probably about 20 patients out of 300) wished to know nothing about the schedule, but just to follow instructions; some of these also entered a clinical trial of withdrawal. For this group (with their consent or by their own request), dummy tablets were gradually substituted for the benzodiazepines. This method was also successful and at the end of the process the patients were amazed and delighted when they found they had been off benzodiazepines and taking only dummy tablets for the last 4 weeks. There are more ways than one of killing a cat, as they say!

FURTHER READING

- Ashton, H. (1994) The treatment of benzodiazepine dependence. Addiction 89;1535-1541.

- Trickett, S. (1998) Coming off Tranquillisers, Sleeping Pills and Antidepressants. Thorsons, London.

SLOW WITHDRAWAL SCHEDULES

A variety of withdrawal schedules from several benzodiazepines are illustrated on the following pages. Schedules such as these have worked on real people, but you may need to adapt them for your own needs. Reference to Table 1, Chapter I, which shows the equivalent strengths of different benzodiazepines, should enable you to work out your own programme and to devise an appropriate schedule for benzodiazepines such as prazepam (Centrax) and quazepam (Doral) and others which are not illustrated.

In my experience, the only exception to the general rule of slow reduction is triazolam (Halcion). This benzodiazepine is eliminated so quickly (half-life 2 hours) that you are practically withdrawn each day, after a dose the night before. For this reason, triazolam can be stopped abruptly without substitution of a long-acting benzodiazepine. If withdrawal symptoms occur, you could take a short course of diazepam starting at about 10mg, decreasing the dosage as shown on Schedule 2. The same approach applies to the non-benzodiazepines zolpidem and zaleplon which both have half-lives of 2 hours.

Slow Withdrawal Schedules »

CHAPTER II

SLOW WITHDRAWAL SCHEDULES

A variety of withdrawal schedules from several benzodiazepines are illustrated below. Schedules such as these have worked on real people, but you may need to adapt them for your own needs. Reference to Table 1, Chapter I, which shows the equivalent strengths of different benzodiazepines, should enable you to work out your own programme and to devise an appropriate schedule for benzodiazepines such as prazepam (Centrax) and quazepam (Doral) and others which are not illustrated.

In my experience, the only exception to the general rule of slow reduction is triazolam (Halcion). This benzodiazepine is eliminated so quickly (half-life 2 hours) that you are practically withdrawn each day, after a dose the night before. For this reason, triazolam can be stopped abruptly without substitution of a long-acting benzodiazepine. If withdrawal symptoms occur, you could take a short course of diazepam starting at about 10mg, decreasing the dosage as shown on Schedule 2.

The same approach applies to the non-benzodiazepines zolpidem and zaleplon which both have half-lives of 2 hours.

Schedule 1. Withdrawal from high dose (6mg) alprazolam (Xanax daily with diazepam (Valium) substitution. (6mg alprazolam is approximately equivalent to 120mg diazepam)

	Morning	**Midday/Afternoon**	**Evening/Night**	**Daily Diazepam Equivalent**
Starting dosage	alprazolam 2mg	alprazolam 2mg	alprazolam 2mg	120mg
Stage 1 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1.5mg diazepam 10mg	120mg
Stage 2 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 3 (one week)	alprazolam 1.5mg diazepam 10mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 4 (one week)	alprazolam 1mg diazepam 20mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 5 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 1mg diazepam 20mg	110mg
Stage 6 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 0.5mg diazepam 20mg	100mg
Stage 7 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	Stop alprazolam diazepam 20mg	90mg
Stage 8 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 1mg diazepam 10mg	diazepam 20mg	80mg

Stage 9 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 0.5mg diazepam 10mg	diazepam 20mg	80mg
Stage 10 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	Stop alprazolam diazepam 10mg	diazepam 20mg	60mg
Stage 11 (1-2 weeks)	Stop alprazolam diazepam 20mg	diazepam 10mg	diazepam 20mg	50mg
Stage 12 (1-2 weeks)	diazepam 25mg	Stop midday dose; divert 5mg each to morning and night doses	diazepam 25mg	50mg
Stage 13 (1-2 weeks)	diazepam 20mg	--	diazepam 25mg	45mg
Stage 14 (1-2 weeks)	diazepam 20mg	--	diazepam 20mg	40mg

Continue as on Schedule 2, reducing from diazepam 40mg

Schedule 1 Notes:

1. There is no actual withdrawal (only diazepam substitution) in Stages 1-4, so these could be undertaken at weekly intervals (but you could take 2 weeks for each stage if preferred).
2. The evening dose of diazepam could be taken at bed-time, rather than with the alprazolam if that is usually taken earlier. (Do not take any other sleeping tablet).
3. Some dosage reduction occurs in later stages of the diazepam switchover (Stages 5-11), so these stages could be undertaken at two week intervals. Even at reducing doses, the diazepam should cover withdrawal from alprazolam, because by this time it has had time to work through the body and will be acting smoothly both day and night. The aim is to obtain a dose of diazepam which avoids withdrawal symptoms but is not so great as to make you sleepy.
4. At Stage 12 it would be sensible to move to twice daily dosage. Diazepam is long-acting and there is no need to take it more than twice a day. There is no reduction in dosage while you make this change (Stages 11 and 12).

Schedule 2. Simple withdrawal from diazepam (Valium) 40mg daily (follow this schedule to complete Schedule 1)

	Morning	**Night**	**Total Daily Dosage**
Starting dosage	diazepam 20mg	diazepam 20mg	40mg
Stage 1 (1-2 weeks)	diazepam 18mg	diazepam 20mg	38mg
Stage 2 (1-2 weeks)	diazepam 18mg	diazepam 18mg	36mg
Stage 3 (1-2 weeks)	diazepam 16mg	diazepam 18mg	34mg
Stage 4 (1-2 weeks)	diazepam 16mg	diazepam 16mg	32mg
Stage 5 (1-2 weeks)	diazepam 14mg	diazepam 16mg	30mg
Stage 6 (1-2 weeks)	diazepam 14mg	diazepam 14mg	28mg
Stage 7 (1-2 weeks)	diazepam 12mg	diazepam 14mg	26mg
Stage 8 (1-2 weeks)	diazepam 12mg	diazepam 12mg	24mg
Stage 9 (1-2 weeks)	diazepam 10mg	diazepam 12mg	22mg
Stage 10 (1-2 weeks)	diazepam 10mg	diazepam 10mg	20mg
Stage 11 (1-2 weeks)	diazepam 8mg	diazepam 10mg	18mg
Stage 12 (1-2 weeks)	diazepam 8mg	diazepam 8mg	16mg
Stage 13 (1-2 weeks)	diazepam 6mg	diazepam 8mg	14mg

Stage 14 (1-2 weeks)	diazepam 5mg	diazepam 8mg	13mg
Stage 15 (1-2 weeks)	diazepam 4mg	diazepam 8mg	12mg
Stage 16 (1-2 weeks)	diazepam 3mg	diazepam 8mg	11mg
Stage 17 (1-2 weeks)	diazepam 2mg	diazepam 8mg	10mg
Stage 18 (1-2 weeks)	diazepam 1mg	diazepam 8mg	9mg
Stage 19 (1-2 weeks)	--	diazepam 8mg	8mg
Stage 20 (1-2 weeks)	--	diazepam 7mg	7mg
Stage 21 (1-2 weeks)	--	diazepam 6mg	6mg
Stage 22 (1-2 weeks)	--	diazepam 5mg	5mg
Stage 23 (1-2 weeks)	--	diazepam 4mg	4mg
Stage 24 (1-2 weeks)	--	diazepam 3mg	3mg
Stage 25 (1-2 weeks)	--	diazepam 2mg	2mg
Stage 26 (1-2 weeks)	--	diazepam 1mg	1mg

Schedule 2 Notes:

1. You could probably manage Stages 1-5 (or even Stages 1-10) in weekly intervals (but take 2 weeks between stages if you prefer).
2. The later stages are probably better taken in 2 week intervals.
3. When you get down to a dose of 5mg daily, you could begin to decrease in 0.5mg doses, but most people manage with 1mg reductions.
4. You will need to utilise a mixture of 10mg, 5mg, and 2mg diazepam tablets to obtain the required dosages. Halve the (scored) 2mg tablet to obtain 1mg doses.

5. If your starting dose is 20mg diazepam daily, you could begin at Stage 10, but in this case you could reduce by 1mg every 2 weeks.
6. If starting from Schedule 1 (alprazolam 6mg daily) continue your reduction using this schedule.

Schedule 3. Withdrawal from lorazepam (Ativan) 6mg daily with diazepam (Valium) substitution. (6mg lorazepam is approximately equivalent to 60mg diazepam)

	Morning	Midday/Afternoon	Evening/Night	Daily Diazepam Equivalent
Starting dosage	lorazepam 2mg	lorazepam 2mg	lorazepam 2mg	60mg
Stage 1 (one week)	lorazepam 2mg	lorazepam 2mg	lorazepam 1mg diazepam 10mg	60mg
Stage 2 (one week)	lorazepam 1.5mg diazepam 5mg	lorazepam 2mg	lorazepam 1mg diazepam 10mg	60mg
Stage 3 (one week)	lorazepam 1.5mg diazepam 5mg	lorazepam 2mg	lorazepam 0.5mg diazepam 15mg	60mg
Stage 4 (one week)	lorazepam 1.5mg diazepam 5mg	lorazepam 1.5mg diazepam 5mg	lorazepam 0.5mg diazepam 15mg	60mg
Stage 5 (1-2 weeks)	lorazepam 1.5mg diazepam 5mg	lorazepam 1.5mg diazepam 5mg	Stop lorazepam diazepam 20mg	60mg
Stage 6 (1-2 weeks)	lorazepam 1mg diazepam 5mg	lorazepam 1.5mg diazepam 5mg	diazepam 20mg	55mg
Stage 7 (1-2 weeks)	lorazepam 1mg diazepam 5mg	lorazepam 1mg diazepam 5mg	diazepam 20mg	50mg
Stage 8 (1-2 weeks)	lorazepam 0.5mg diazepam 5mg	lorazepam 1mg diazepam 5mg	diazepam 20mg	45mg

Stage 9 (1-2 weeks)	lorazepam 0.5mg diazepam 5mg	lorazepam 0.5mg diazepam 5mg	diazepam 20mg	40mg
Stage 10 (1-2 weeks)	Stop lorazepam diazepam 5mg	lorazepam 0.5mg diazepam 5mg	diazepam 20mg	35mg
Stage 11 (1-2 weeks)	diazepam 5mg	Stop lorazepam diazepam 5mg	diazepam 20mg	30mg
Stage 12 (1-2 weeks)	diazepam 5mg	diazepam 5mg	diazepam 18mg	28mg
Stage 13 (1-2 weeks)	diazepam 5mg	diazepam 5mg	diazepam 16mg	26mg
Stage 14 (1-2 weeks)	diazepam 5mg	diazepam 5mg	diazepam 14mg	24mg
Stage 15 (1-2 weeks)	diazepam 5mg	diazepam 5mg	diazepam 12mg	22mg
Stage 16 (1-2 weeks)	diazepam 5mg	diazepam 5mg	diazepam 10mg	20mg
Stage 17 (1-2 weeks)	diazepam 5mg	diazepam 4mg	diazepam 10mg	19mg
Stage 18 (1-2 weeks)	diazepam 4mg	diazepam 4mg	diazepam 10mg	18mg
Stage 19 (1-2 weeks)	diazepam 4mg	diazepam 3mg	diazepam 10mg	17mg
Stage 20 (1-2 weeks)	diazepam 3mg	diazepam 3mg	diazepam 10mg	16mg
Stage 21 (1-2 weeks)	diazepam 3mg	diazepam 2mg	diazepam 10mg	15mg

Stage 22 (1-2 weeks)	diazepam 2mg	diazepam 2mg	diazepam 10mg	14mg
Stage 23 (1-2 weeks)	diazepam 2mg	diazepam 1mg	diazepam 10mg	13mg
Stage 24 (1-2 weeks)	diazepam 1mg	diazepam 1mg	diazepam 10mg	12mg
Stage 25 (1-2 weeks)	diazepam 1mg	Stop diazepam	diazepam 10mg	11mg
Stage 26 (1-2 weeks)	Stop diazepam	--	diazepam 10mg	10mg
Stage 27 (1-2 weeks)	--	--	diazepam 9mg	9mg
Stage 28 (1-2 weeks)	--	--	diazepam 8mg	8mg
Stage 29 (1-2 weeks)	--	--	diazepam 7mg	7mg
Stage 30 (1-2 weeks)	--	--	diazepam 6mg	6mg
Stage 31 (1-2 weeks)	--	--	diazepam 5mg	5mg
Stage 32 (1-2 weeks)	--	--	diazepam 4mg	4mg
Stage 33 (1-2 weeks)	--	--	diazepam 3mg	3mg
Stage 34 (1-2 weeks)	--	--	diazepam 2mg	2mg

Stage 35 (1-2 weeks)	--	--	diazepam 1mg	1mg
Stage 36	--	--	Stop diazepam	--

Schedule 3 Notes:

1. There is no actual withdrawal (only diazepam substitution) in Stages 1-5, so these could be undertaken at weekly intervals (but you could take 2 weeks if preferred).
2. The evening dose of diazepam could be taken at bed-time, rather than with the lorazepam if that is usually taken earlier. (Do not take any other sleeping tablet).
3. Some dosage reduction occurs during the later stages of the diazepam switchover (Stages 6-11), so these stages could be undertaken at two week intervals. Even at reducing doses, the diazepam should cover withdrawal from lorazepam, because by this time it has had time to work through the body and will be acting smoothly both day and night. The aim is to obtain a dose of diazepam which avoids withdrawal symptoms but is not so great as to make you sleepy.
4. Day-time doses of diazepam are gradually phased out (Stages 17-25); in succeeding stages you only need to phase out the night-time dose by 1mg every week or two.
5. A mixture of 10mg, 5mg and 2mg diazepam tablets will be needed to obtain the required doses. Halve the (scored) 2mg tablets to obtain 1mg doses.

Schedule 4. Withdrawal from nitrazepam (Mogadon) 10mg at night with diazepam (Valium) substitution. (Nitrazepam is approximately the same strength as diazepam)

	Bed-time dose
Starting dosage	nitrazepam 10mg
Stage 1 (1 week)	nitrazepam 5mg diazepam 5mg
Stage 2 (1 week)	Stop nitrazepam diazepam 10mg
Stage 3 (1-2 weeks)	diazepam 9mg

Stage 4 (1-2 weeks)	diazepam 8mg
Stage 5 (1-2 weeks)	diazepam 7mg
Stage 6 (1-2 weeks)	diazepam 6mg
Stage 7 (1-2 weeks)	diazepam 5mg
Stage 8 (1-2 weeks)	diazepam 4mg
Stage 9 (1-2 weeks)	diazepam 3mg
Stage 10 (1-2 weeks)	diazepam 2mg
Stage 11 (1-2 weeks)	diazepam 1mg
Stage 12	Stop diazepam

Schedule 4 Notes:

- If you are taking more than 10mg nitrazepam, replace each 5mg nitrazepam, one at a time, with 5mg diazepam, then reduce the diazepam in 1mg or 2mg stages.

Schedule 5. Withdrawal from clonazepam (Klonopin) 1.5mg daily with substitution of diazepam (Valium). (0.5mg clonazepam is approximately equivalent to 10mg diazepam)

	Morning	Midday/Afternoon	Evening/Night	Daily Diazepam Equivalent
Starting dosage	clonazepam 0.5mg	clonazepam 0.5mg	clonazepam 0.5mg	30mg

Stage 1 (1 week)	clonazepam 0.5mg	clonazepam 0.5mg	clonazepam 0.25mg diazepam 5mg	30mg
Stage 2 (1 week)	clonazepam 0.5mg	clonazepam 0.5mg	Stop clonazepam diazepam 10mg	30mg
Stage 3 (1 week)	clonazepam 0.25mg diazepam 5mg	clonazepam 0.5mg	diazepam 10mg	30mg
Stage 4 (1 week)	clonazepam 0.25mg diazepam 5mg	clonazepam 0.25mg diazepam 5mg	diazepam 10mg	30mg
Stage 5 (1 week)	Stop clonazepam diazepam 10mg	clonazepam 0.25mg diazepam 5mg	diazepam 10mg	30mg
Stage 6 (1-2 weeks)	diazepam 10mg	Stop clonazepam diazepam 8mg	diazepam 10mg	28mg
Stage 7 (1-2 weeks)	diazepam 10mg	diazepam 6mg	diazepam 10mg	26mg
Stage 8 (1-2 weeks)	diazepam 10mg	diazepam 4mg	diazepam 10mg	24mg
Stage 9 (1-2 weeks)	diazepam 10mg	diazepam 2mg	diazepam 10mg	22mg
Stage 10 (1-2 weeks)	diazepam 10mg	Stop diazepam	diazepam 10mg	20mg
Stage 11 (1-2 weeks)	diazepam 8mg	--	diazepam 10mg	18mg
Stage 12 (1-2 weeks)	diazepam 6mg	--	diazepam 10mg	16mg
Stage 13 (1-2 weeks)	diazepam 4mg	--	diazepam 10mg	14mg

Stage 14 (1-2 weeks)	diazepam 2mg	--	diazepam 10mg	12mg
Stage 15 (1-2 weeks)	Stop diazepam	--	diazepam 10mg	10mg
Continue reducing remaining diazepam by 1 mg every 2 weeks (see Schedule 3 Stage 26)				

Schedule 6. Withdrawal from clonazepam (Klonopin) 3mg daily with substitution of diazepam (Valium). (1 mg clonazepam is equivalent to 20mg diazepam)

	Morning	**Midday/Afternoon**	**Evening/Night**	**Daily Diazepam Equivalent**
Starting dosage	clonazepam 1mg	clonazepam 1mg	clonazepam 1mg	60mg
Stage 1 (1-2 weeks)	clonazepam 1mg	clonazepam 1mg	clonazepam 0.5mg diazepam 10mg	60mg
Stage 2 (1-2 weeks)	clonazepam 0.5mg diazepam 10mg	clonazepam 1mg	clonazepam 0.5mg diazepam 10mg	60mg
Stage 3 (1-2 weeks)	clonazepam 0.5mg diazepam 10mg	clonazepam 0.5mg diazepam 5mg	clonazepam 0.5mg diazepam 10mg	55mg
Stage 4 (1-2 weeks)	clonazepam 0.5mg diazepam 10mg	clonazepam 0.5mg diazepam 5mg	Stop clonazepam diazepam 15mg	50mg
Stage 5 (1-2 weeks)	clonazepam 0.25mg diazepam 10mg	clonazepam 0.5mg diazepam 5mg	diazepam 15mg	45mg
Stage 6 (1-2 weeks)	clonazepam 0.25mg diazepam 10mg	clonazepam 0.25mg diazepam 5mg	diazepam 15mg	40mg

Stage 7 (1-2 weeks)	Stop clonazepam diazepam 10mg	clonazepam 0.25mg diazepam 5mg	diazepam 15mg	35mg
Stage 8 (1-2 weeks)	diazepam 10mg	Stop clonazepam diazepam 5mg	diazepam 15mg	30mg
Stage 9 (1-2 weeks)	diazepam 10mg	diazepam 2.5mg	diazepam 15mg	27.5mg
Stage 10 (1-2 weeks)	diazepam 12mg	Stop diazepam	diazepam 15mg	27mg
Stage 11 (1-2 weeks)	diazepam 10mg	--	diazepam 15mg	25mg
Stage 12 (1-2 weeks)	diazepam 10mg	--	diazepam 14mg	24mg
Stage 13 (1-2 weeks)	diazepam 10mg	--	diazepam 12mg	22mg
Stage 14 (1-2 weeks)	diazepam 10mg	--	diazepam 10mg	20mg
Continue from Schedule 5, Stage 10				

Schedule 6 Notes:

- The small reduction (27.5mg to 27mg) between Stages 9 and 10 is to allow you to adjust to twice daily dose.

Schedule 7. Withdrawal from alprazolam (Xanax) 4mg daily with diazepam (Valium) substitution (4mg alprazolam is approximately equivalent to 80mg diazepam)

	Morning	**Midday**	**Afternoon**	**Evening**	**Daily Diazepam Equivalent**

Starting dosage	alprazolam 1mg	alprazolam 1mg	alprazolam 1mg	alprazolam 1mg	80mg
Stage 1 (1 week)	alprazolam 1mg	alprazolam 1mg	alprazolam 1mg	alprazolam 0.5mg diazepam 10mg	80mg
Stage 2 (1 week)	alprazolam 1mg	alprazolam 0.5mg diazepam 10mg	alprazolam 1mg	alprazolam 0.5mg diazepam 10mg	80mg
Stage 3 (1 week)	alprazolam 0.5mg diazepam 10mg	alprazolam 0.5mg diazepam 10mg	alprazolam 1mg	alprazolam 0.5mg diazepam 10mg	80mg
Stage 4 (1 week)	alprazolam 0.5mg diazepam 10mg	alprazolam 0.5mg diazepam 10mg	alprazolam 0.5mg diazepam 10mg	alprazolam 0.5mg diazepam 10mg	80mg
Stage 5 (1 week)	alprazolam 0.5mg diazepam 10mg	alprazolam 0.5mg diazepam 10mg	alprazolam 0.5mg diazepam 10mg	alprazolam 0.5mg diazepam 10mg	80mg
Stage 6 (1-2 weeks)	alprazolam 0.5mg diazepam 10mg	alprazolam 0.25mg diazepam 10mg	alprazolam 0.5mg diazepam 10mg	diazepam 20mg	75mg
Stage 7 (1-2 weeks)	alprazolam 0.25mg diazepam 10mg	alprazolam 0.25mg diazepam 10mg	alprazolam 0.5mg diazepam 10mg	diazepam 20mg	70mg
Stage 8 (1-2 weeks)	alprazolam 0.25mg diazepam 10mg	alprazolam 0.25mg diazepam 10mg	alprazolam 0.25mg diazepam 10mg	diazepam 20mg	65mg
Stage 9 (1-2 weeks)	alprazolam 0.25mg diazepam 10mg	Stop alprazolam diazepam 10mg	alprazolam 0.25mg diazepam 10mg	diazepam 20mg	60mg
Stage 10 (1-2 weeks)	Stop alprazolam diazepam 10mg	diazepam 10mg	alprazolam 0.25mg diazepam 10mg	diazepam 20mg	55mg

Stage 11 (1-2 weeks)	diazepam 10mg	diazepam 10mg	Stop alprazolam diazepam 10mg	diazepam 20mg	50mg
Stage 12 (1-2 weeks)	diazepam 10mg	diazepam 5mg	diazepam 10mg	diazepam 20mg	45mg
Stage 13 (1-2 weeks)	diazepam 5mg	diazepam 5mg	diazepam 10mg	diazepam 20mg	40mg
Stage 14 (1-2 weeks)	diazepam 5mg	diazepam 5mg	diazepam 5mg	diazepam 20mg	35mg
Stage 15 (1-2 weeks)	diazepam 5mg	diazepam 5mg	diazepam 5mg	diazepam 15mg	30mg
Stage 16 (1-2 weeks)	diazepam 5mg	diazepam 5mg	diazepam 5mg	diazepam 12.5mg	27.5mg
Stage 17 (1-2 weeks)	diazepam 5mg	diazepam 5mg	diazepam 5mg	diazepam 10mg	25mg
Stage 18 (1-2 weeks)	diazepam 5mg	diazepam 2.5mg	diazepam 5mg	diazepam 10mg	22.5mg
Stage 19 (1-2 weeks)	diazepam 5mg	Stop diazepam	diazepam 5mg	diazepam 10mg	20mg
Stage 20 (1-2 weeks)	diazepam 4mg	--	diazepam 5mg	diazepam 10mg	19mg
Stage 21 (1-2 weeks)	diazepam 4mg	--	diazepam 4mg	diazepam 10mg	18mg
Stage 22 (1-2 weeks)	diazepam 4mg	--	diazepam 3mg	diazepam 10mg	17mg
Stage 23 (1-2 weeks)	diazepam 3mg	--	diazepam 3mg	diazepam 10mg	16mg

Stage 24 (1-2 weeks)	diazepam 3mg	--	diazepam 2mg	diazepam 10mg	15mg
Stage 25 (1-2 weeks)	diazepam 2mg	--	diazepam 2mg	diazepam 10mg	14mg
Stage 26 (1-2 weeks)	diazepam 2mg	--	Stop diazepam	diazepam 10mg	12mg
Stage 27 (1-2 weeks)	Stop diazepam	--	--	diazepam 10mg	10mg
Continue reducing diazepam by 1mg every 2 weeks (see Schedule 3, Stage 26)					

Schedule 7 Notes:

- The evening diazepam dose can be taken at bed-time, rather than with alprazolam if that is usually taken earlier.

Schedule 8. Withdrawal from lorazepam (Ativan) 3mg daily with diazepam (Valium) substitution. (3mg lorazepam is approximately equivalent to 30mg diazepam)

	Morning	**Midday/Afternoon**	**Evening/Night**	**Daily Diazepam Equivalent**
Starting dosage	lorazepam 1 mg	lorazepam 1 mg	lorazepam 1 mg	30mg
Stage 1 (1 week)	lorazepam 1 mg	lorazepam 1 mg	lorazepam 0.5mg diazepam 5mg	30mg
Stage 2 (1 week)	lorazepam 0.5mg diazepam 5mg	lorazepam 1 mg	lorazepam 0.5mg diazepam 5mg	30mg
Stage 3 (1 week)	lorazepam 0.5mg diazepam 5mg	lorazepam 0.5mg diazepam 5mg	lorazepam 0.5mg diazepam 5mg	30mg

Stage 4 (1 week)	lorazepam 0.5mg diazepam 5mg	lorazepam 0.5mg diazepam 5mg	Stop lorazepam diazepam 10mg	30mg
Stage 5 (1 week)	Stop lorazepam diazepam 10mg	lorazepam 0.5mg diazepam 5mg	diazepam 10mg	30mg
Stage 6 (1 week)	diazepam 10mg	Stop lorazepam diazepam 10mg	diazepam 10mg	30mg
Stage 7 (1-2 weeks)	diazepam 10mg	diazepam 8mg	diazepam 10mg	28mg
Stage 8 (1-2 weeks)	diazepam 8mg	diazepam 8mg	diazepam 10mg	26mg
Stage 9 (1-2 weeks)	diazepam 8mg	diazepam 6mg	diazepam 10mg	24mg
Stage 10 (1-2 weeks)	diazepam 6mg	diazepam 6mg	diazepam 10mg	22mg
Stage 11 (1-2 weeks)	diazepam 6mg	diazepam 4mg	diazepam 10mg	20mg
Stage 12 (1-2 weeks)	diazepam 6mg	diazepam 2mg	diazepam 10mg	18mg
Stage 13 (1-2 weeks)	diazepam 6mg	Stop diazepam	diazepam 10mg	16mg
Stage 14 (1-2 weeks)	diazepam 5mg	--	diazepam 10mg	15mg
Stage 15 (1-2 weeks)	diazepam 4mg	--	diazepam 10mg	14mg
Stage 16 (1-2 weeks)	diazepam 3mg	--	diazepam 10mg	13mg

Stage 17 (1-2 weeks)	diazepam 2mg	--	diazepam 10mg	12mg
Stage 18 (1-2 weeks)	diazepam 1mg	--	diazepam 10mg	11mg
Stage 19 (1-2 weeks)	Stop diazepam	--	diazepam 10mg	10mg
Continue reducing night time diazepam by 1 mg every 1-2 weeks (See Schedule 3, Stage 26)				

Schedule 9. Withdrawal from temazepam (Restoril) 30mg nightly with diazepam substitution. (30mg temazepam is approximately equivalent to 15mg diazepam)

	Night time	**Equivalent diazepam dosage**
Starting dosage	temazepam 30mg	15mg
Stage 1 (1-2 weeks)	temazepam 15mg diazepam 7.5mg	15mg
Stage 2 (1-2 weeks)	temazepam 7.5mg diazepam 12mg	15.75mg
Stage 3 (1-2 weeks)	Stop temazepam diazepam 15mg	15mg
Stage 4 (1-2 weeks)	diazepam 14mg	14mg
Stage 5 (1-2 weeks)	diazepam 13mg	13mg
Stage 6 (1-2 weeks)	diazepam 12mg	12mg

Stage 7 (1-2 weeks)	diazepam 11mg	11mg
Stage 8 (1-2 weeks)	diazepam 10mg	10mg
Stage 9 (1-2 weeks)	diazepam 9mg	9mg
Stage 10 (1-2 weeks)	diazepam 8mg	8mg
Stage 11 (1-2 weeks)	diazepam 7mg	7mg
Stage 12 (1-2 weeks)	diazepam 6mg	6mg
Stage 13 (1-2 weeks)	diazepam 5mg	5mg
Stage 14 (1-2 weeks)	diazepam 4mg	4mg
Stage 15 (1-2 weeks)	diazepam 3mg	3mg
Stage 16 (1-2 weeks)	diazepam 2mg	2mg
Stage 17 (1-2 weeks)	diazepam 1mg	1mg
Stage 18	Stop diazepam	--

Schedule 10. Withdrawal from oxazepam (Serax) 20mg three times daily (60mg) with diazepam (Valium) substitution (20mg oxazepam is approximately equivalent to 10mg diazepam)

	Morning	Midday	Evening/Night	Daily Diazepam Equivalent

Starting dosage	oxazepam 20mg	oxazepam 20mg	oxazepam 20mg	30mg
Stage 1 (1 week)	oxazepam 20mg	oxazepam 20mg	oxazepam 10mg diazepam 5mg	30mg
Stage 2 (1 week)	oxazepam 10mg diazepam 5mg	oxazepam 20mg	oxazepam 10mg diazepam 5mg	30mg
Stage 3 (1 week)	oxazepam 10mg diazepam 5mg	oxazepam 10mg diazepam 5mg	oxazepam 10mg diazepam 5mg	30mg
Stage 4 (1-2 weeks)	oxazepam 10mg diazepam 5mg	oxazepam 10mg diazepam 5mg	Stop oxazepam diazepam 8mg	28mg
Stage 5 (1-2 weeks)	Stop oxazepam diazepam 8mg	oxazepam 10mg diazepam 5mg	diazepam 8mg	26mg
Stage 6 (1-2 weeks)	diazepam 8mg	Stop oxazepam diazepam 8mg	diazepam 8mg	24mg
Stage 7 (1-2 weeks)	diazepam 10mg	diazepam 2mg	diazepam 10mg	22mg
Stage 8 (1-2 weeks)	diazepam 10mg	Stop diazepam	diazepam 10mg	20mg
Stage 9 (1-2 weeks)	diazepam 8mg	--	diazepam 10mg	18mg
Continue as on Schedule 2 from Stage 12				

Schedule 10 Notes:

1. Oxazepam is short-acting (half-life 4-15 hrs) so substitution to diazepam (long-acting) is recommended.
2. Diazepam need only be taken twice a day.
3. A change from 5mg to 2mg diazepam tablets is necessary from Stage 4 onwards.

Schedule 11. Withdrawal from chlordiazepoxide (Librium) 25mg three times daily (75mg). (25mg chlordiazepoxide is approximately equivalent to 10mg diazepam)

	Morning	**Midday**	**Evening/Night**
Starting dosage	chlordiazepoxide 25mg	chlordiazepoxide 25mg	chlordiazepoxide 25mg
Stage 1 (1-2 weeks)	chlordiazepoxide 25mg	chlordiazepoxide 20mg	chlordiazepoxide 25mg
Stage 2 (1-2 weeks)	chlordiazepoxide 20mg	chlordiazepoxide 20mg	chlordiazepoxide 25mg
Stage 3 (1-2 weeks)	chlordiazepoxide 20mg	chlordiazepoxide 20mg	chlordiazepoxide 20mg
Stage 4 (1-2 weeks)	chlordiazepoxide 25mg	chlordiazepoxide 5mg	chlordiazepoxide 25mg
Stage 5 (1-2 weeks)	chlordiazepoxide 25mg	Stop chlordiazepoxide	chlordiazepoxide 25mg
Stage 6 (1-2 weeks)	chlordiazepoxide 20mg	--	chlordiazepoxide 25mg
Stage 7 (1-2 weeks)	chlordiazepoxide 20mg	--	chlordiazepoxide 20mg
Stage 8 (1-2 weeks)	chlordiazepoxide 15mg	--	chlordiazepoxide 20mg
Stage 9 (1-2 weeks)	chlordiazepoxide 15mg	--	chlordiazepoxide 15mg
Stage 10 (1-2 weeks)	chlordiazepoxide 10mg	--	chlordiazepoxide 15mg

Stage 11 (1-2 weeks)	chlordiazepoxide 10mg	--	chlordiazepoxide 10mg
Stage 12 (1-2 weeks)	chlordiazepoxide 5mg	--	chlordiazepoxide 10mg
Stage 13 (1-2 weeks)	chlordiazepoxide 5mg	--	chlordiazepoxide 5mg
Stage 14 (1-2 weeks)	chlordiazepoxide 2.5mg (½ tablet)	--	chlordiazepoxide 5mg
Stage 15 (1-2 weeks)	chlordiazepoxide 2.5mg (½ tablet)	--	chlordiazepoxide 2.5mg (½ tablet)
Stage 16 (1-2 weeks)	Stop chlordiazepoxide	--	chlordiazepoxide 2.5mg (½ tablet)
Stage 17	--	--	Stop chlordiazepoxide

Schedule 11 Notes:

1. Chlordiazepoxide is long-acting so there is no need to take it more frequently than twice a day (hence Stages 4 and 5).
2. Because chlordiazepoxide is long-acting, there is no need for diazepam substitution.
3. If you are taking chlordiazepoxide capsules, change to tablets which can be halved for stages 14 onwards.

Schedule 12. Withdrawal from zopiclone (Zimovane) 15mg with diazepam (Valium) substitution. (15mg zopiclone is approximately equivalent to 10mg diazepam)

	Night time	**Daily Diazepam Equivalent**
Starting dosage	zopiclone 15mg	10mg

Stage 1 (1 week)	zopiclone 7.5mg diazepam 5mg	10mg
Stage 2 (1 week)	Stop zopiclone diazepam 10mg	10mg
Stage 3 (1-2 weeks)	diazepam 9mg	9mg
Stage 4 (1-2 weeks)	diazepam 8mg	8mg
Then continue reducing diazepam by 1mg every 1-2 weeks as on Schedule 2		

Schedule 12 Notes:

1. It is possible to withdraw directly from zopiclone using the smallest available tablets (3.75mg), but this dose of zopiclone is equivalent to 2.5mg diazepam making for rather abrupt dosage reductions.
2. This method can also be used for withdrawing from loprazolam and lormetazepam. 1mg of each of these is approximately equivalent to 10mg diazepam; their half-lives are 6-12 and 10-12 hrs respectively.

Schedule 13. Antidepressant Withdrawal Table

Drugs	**Dosage strengths and formulations***
Tricyclics	
amitriptyline (Tryptizol, Elavil)	tabs 10, 25, 50mg; liquid 25mg/5ml
amoxapine (Asendis)	tabs 25, 50, 100mg
clomipramine (Anafranil)	caps 10, 25, 50mg; syrup 25mg/5ml
dothiepin (Prothiaden)	tabs 25, 75mg

doxepin (Sinequan)	caps 10, 25, 50, 75mg
imipramine (Tofranil)	tabs 10, 25mg syrup 25mg/5ml
lofepramine (Gamanil)	tabs 70mg; liquid 70mg/5ml
nortriptyline (Allegron, Pamelor)	tabs 10, 25mg
protriptyline (Concordin, Vivactil)	tabs 5, 10mg
trimipramine (Surmontil)	tabs 10, 25mg
Related antidepressants	
maprotiline (Ludiomil)	tabs 10, 25, 50, 75mg
mianserin (Bolvidon, Norval)	tabs 10, 30mg
trazodone (Molipaxin, Desyrel)	caps 50, 100mg; tabs 150mg; liquid 50mg/5ml
viloxazine (Vivalan)	tabs 50mg
MAOIs (monoamine oxidase inhibitors)	
phenelzine (Nardil)	tabs 15mg
moclobemide (Mannerix)	tabs 150mg
tranylcypromine (Parnate)	tabs 10mg
SSRIs (selective serotonin reuptake inhibitors)	

citalopram (Cipramil, Celexa)	tabs 10, 20, 40mg; liquid 40mg/ml (drops)
fluoxetine (Prozac)	caps 20, 60mg; liquid 20mg/5ml
fluvoxamine (Faverin, Luvox)	tabs(s) 50, 100mg
paroxetine (Seroxat, Paxil)	tabs(s) 20, 30mg; liquid 20mg/5ml
sertraline (Lustral, Zoloft)	tabs 50, 100mg
escitalopram (Cipralex, Lexapro)	tabs 5, 10(s), 20mg(s)
Others	
mirtazapine (Zispin, Remeron)	tabs(s) 30mg
nefazodone (Dutonin, Serzone)	tabs(s) 100, 200mg
reboxetine (Edronax, Vestra)	tabs(s) 4mg
venlafaxine (Efexor, Effexor)	tabs 37.5, 75mg
* tabs: tablets, (s) scored; caps: capsules; 5ml = 1 teaspoon	

Schedule 13 Notes:

Guidelines for benzodiazepine users who are also taking an antidepressant and wish to withdraw from both drugs

1) Complete the benzodiazepine withdrawal before starting to taper the antidepressant.
2) Allow at least 4 weeks after stopping benzodiazepines before starting on antidepressant withdrawal.
3) Consult your doctor before starting to withdraw the antidepressant and agree on a tapering schedule.
4) Antidepressant withdrawal must be gradual to avoid withdrawal effects.
    a) Make each dose reduction as small as possible, e.g. by halving the tablets or using a liquid preparation.

b) If smaller doses are not available, reduce by taking a tablet every other day, then every third day, etc.
c) Allow 1-2 weeks between each dosage reduction.
d) If withdrawal symptoms are severe (Chapter 3, Table 2) increase the dosage slightly (e.g. to the dose at your last reduction). When symptoms have settled, resume withdrawal at a slower rate.

5) With slow tapering, as outlined above, withdrawal symptoms from antidepressants are usually absent, or if they occur, are mild and short-lived.

CHAPTER III

BENZODIAZEPINE WITHDRAWAL SYMPTOMS, ACUTE AND PROTRACTED

Chapter I described what benzodiazepines do when they are in the body and how tolerance and dependence develop. Chapter II discussed the need for slow withdrawal and gave practical examples of dosage tapering. This chapter is concerned with what happens as benzodiazepines leave the body in the course of withdrawal and afterwards. The focus is on withdrawal symptoms, and how to cope with them if they occur.

It cannot be too strongly stressed that withdrawal symptoms can be minimised and largely avoided by slow tapering, tailored to the individual's needs as outlined in Chapter II. However, some long-term benzodiazepine users begin to experience "withdrawal" symptoms even though they continue taking the drug. This is due to the development of drug tolerance (Chapter I) which sometimes leads doctors to increase the dosage or add another benzodiazepine. Analysis of the first 50 patients who attended my benzodiazepine withdrawal clinic showed that all of them had symptoms on first presentation while still on benzodiazepines (12 of them were taking two prescribed benzodiazepines at once). Their symptoms included the full range of psychological and physical symptoms usually described as benzodiazepine withdrawal symptoms. The process of slow benzodiazepine tapering in these patients caused only slight exacerbation of these symptoms, which then declined after withdrawal.

People who develop severe symptoms on benzodiazepine withdrawal have usually come off the drugs too rapidly. Lack of explanation of the symptoms has often added to their distress and has introduced fears ("Am I going mad?") which themselves magnify the symptoms. A few, because of these frightening experiences, have ended up with a condition akin to post-traumatic stress disorder (PTSD). But a proper understanding of the reasons for and nature of any symptoms that arise can do much to allay the bewilderment and fear associated with benzodiazepine withdrawal and can also help prevent long-term sequelae. Withdrawal reactions are in fact a normal response to the discontinuation of many chronically used drugs including alcohol, opiates, antipsychotics, antidepressants, and even some medications for angina and hypertension.

Mechanisms of withdrawal reactions. Drug withdrawal reactions in general tend to consist of a mirror image of the drugs' initial effects. In the case of benzodiazepines, sudden cessation after chronic use may result in dreamless sleep being replaced by insomnia and nightmares; muscle relaxation by increased tension and muscle spasms; tranquillity by anxiety and panic; anticonvulsant effects by epileptic seizures. These reactions are caused by the abrupt exposure of adaptations that have occurred in the nervous system in response to the chronic presence of the drug. Rapid removal of the drug opens the floodgates, resulting in rebound overactivity of all the systems which have been damped down by the benzodiazepine and are now no longer opposed. Nearly all the excitatory mechanisms in the nervous system go into overdrive and, until new adaptations to the drug-free state develop, the brain and peripheral nervous system are in a hyperexcitable state, and extremely vulnerable to stress.

Acute withdrawal symptoms. The most prominent effect of benzodiazepines is an anti-anxiety effect - that is why they were developed as tranquillisers. As a consequence, nearly all the acute symptoms of withdrawal are those of anxiety. They have been described in anxiety states in people who have never touched a benzodiazepine and were recognised as psychological and physical symptoms of anxiety long before benzodiazepines were discovered. However, certain symptom clusters are particularly characteristic of benzodiazepine withdrawal. These include hypersensitivity to sensory stimuli (sound, light, touch, taste and smell) and perceptual distortions (for example sensation of the floor undulating, feeling of motion, impressions of walls or floors tilting, sensation of walking on cotton wool). There also appears to be a higher incidence than usually seen in anxiety states of depersonalisation, feelings of unreality, and tingling and numbness. Visual hallucinations, distortion of the body image ("my head feels like a football/balloon"), feelings of insects crawling on the skin, muscle twitching and weight loss are not uncommon in benzodiazepine withdrawal but unusual in anxiety states.

Table 1 gives a list of symptoms which were spontaneously described by patients in my withdrawal clinic. It is clearly a long list and is probably not inclusive. Of course, not all patients get all the symptoms, and none of the symptoms are inevitable. Withdrawal often seems to seek out the individual's most vulnerable points: if he is prone to headaches, worse headaches may feature in withdrawal; if he is prone to "irritable bowel", digestive symptoms may be aggravated. Such symptoms are nearly always temporary and can be minimised. They are less frightening and seem less important or bizarre if their cause is understood. Furthermore, patients can learn techniques to alleviate or control many of the symptoms: there is a lot they can do to help themselves.

TABLE 1. BENZODIAZEPINE WITHDRAWAL SYMPTOMS

PSYCHOLOGICAL SYMPTOMS

- Excitability (jumpiness, restlessness)
- Insomnia, nightmares, other sleep disturbances
- Increased anxiety, panic attacks

Agoraphobia, social phobia
Perceptual distortions
Depersonalisation, derealisation
Hallucinations, misperceptions
Depression
Obsessions
Paranoid thoughts
Rage, aggression, irritability
Poor memory and concentration
Intrusive memories
Craving (rare)

PHYSICAL SYMPTOMS

Headache
Pain/stiffness - (limbs, back, neck, teeth, jaw)
Tingling, numbness, altered sensation - (limbs, face, trunk)
Weakness ("jelly-legs")
Fatigue, influenza-like symptoms
Muscle twitches, jerks, tics, "electric shocks"
Tremor
Dizziness, light-headedness, poor balance
Blurred/double vision, sore or dry eyes
Tinnitus
Hypersensitivity - (light, sound, touch, taste, smell)
Gastrointestinal symptoms - (nausea, vomiting, diarrhoea, constipation, pain, distension, difficulty swallowing)
Appetite/weight change
Dry mouth, metallic taste, unusual smell
Flushing/sweating/palpitations
Overbreathing
Urinary difficulties/menstrual difficulties
Skin rashes, itching
Fits (rare)

These symptoms have all been described by patients withdrawing from benzodiazepines; they are not arranged in any particular order, and few if any are specific to benzodiazepine withdrawal. The list is probably not inclusive. Different individuals experience different combinations of symptoms. Do not expect to get **all** these symptoms!

INDIVIDUAL SYMPTOMS, THEIR CAUSES AND HOW TO DEAL WITH THEM

Insomnia, nightmares, sleep disturbance. The sleep engendered by benzodiazepines, though it may seem refreshing at first, is not a normal sleep. Benzodiazepines inhibit both dreaming sleep (rapid eye movement sleep, REMS) and deep sleep (slow wave sleep, SWS). The extra sleep time that benzodiazepines provide is spent mainly in light sleep, termed Stage 2 sleep. REM and SWS are the two most important stages of sleep and are essential to health.

Sleep deprivation studies show that any deficit is quickly made up by a rebound to above normal levels as soon as circumstances permit.

In regular benzodiazepine users REMS and SWS tend to return to pre-drug levels (because of tolerance) but the initial deficit remains. On withdrawal, even after years of benzodiazepine use, there is a marked rebound increase in REMS which also becomes more intense. As a result, dreams become more vivid, nightmares may occur and cause frequent awakenings during the night. This is a normal reaction to benzodiazepine withdrawal and, though unpleasant, it is a sign that recovery is beginning to take place. When the deficit of REMS is made up, usually after about 4-6 weeks, the nightmares become less frequent and gradually fade away.

Return of SWS seems to take longer after withdrawal, probably because anxiety levels are high, the brain is overactive and it is hard to relax completely. Subjects may have difficulty in getting off to sleep and may experience "restless legs syndrome", sudden muscle jerks (myoclonus) just as they are dropping off or be jolted suddenly by a hallucination of a loud bang (hypnagogic hallucination) which wakes them up again. These disturbances may also last for several weeks, sometimes months.

However, all these symptoms do settle in time. The need for sleep is so powerful that normal sleep will eventually reassert itself. Meanwhile, attention to sleep hygiene measures including avoiding tea, coffee, other stimulants or alcohol near bedtime, relaxation tapes, anxiety management techniques and physical exercise may be helpful. Taking all or most of the dose of benzodiazepine at night during the reduction period may also help. Occasionally another drug might be indicated (see section on adjuvant drugs, below).

Intrusive memories. A fascinating symptom in patients undergoing benzodiazepine withdrawal is that they often mention the occurrence of what seem to be intrusive memories. Their minds will suddenly conjure up a vivid memory of someone they have not thought about or seen for years. Sometimes the other person's face will appear when looking in the mirror. The memory seems uncalled for and may recur, intruding on other thoughts. The interesting thing about these memories is that they often start to occur at the same time that vivid dreams appear; these may be delayed until one or more weeks after the dosage tapering has started. Since recent sleep research indicates that certain stages of sleep (REMS and SWS) are important for memory functions, it is likely that the dreams and the memories are connected. In both cases the phenomena may herald the beginning of a return in normal memory functions and, although sometimes disturbing, can be welcomed as a sign of a step towards recovery.

Poor memory and concentration are also features of benzodiazepine withdrawal, and are probably due to continued effects of the drug. Mentors should be prepared to repeat encouragements again and again, week after week, as their words are soon forgotten.

Panic attacks. Panic attacks may appear for the first time during withdrawal, although some patients have long experience with this distressing symptom. The actress Glenda Jackson, who

was not on benzodiazepines, described them as follows: "God, those panic attacks. You think you're dying; your heart pounds so strongly it feels like it's going to jump out of your chest; you choke and begin to feel you can't breathe - and all this is accompanied by terrible shaking and tremor, and feeling freezing cold" (Sunday Times Magazine p.15, October 17, 1999). These attacks are characteristic of some anxiety states and are the result of storms of central and peripheral nervous system hyperactivity, especially the centres normally concerned with fear and flight reactions in response to emergencies. The brain centres that control these fear reactions have been damped down by benzodiazepines and may rebound with renewed vigour as the benzodiazepines leave the body.

Distressing as they are, panic attacks are never fatal and usually last little more than 30 minutes. What is more, it is possible to learn to exercise control over them. Various approaches are described below. Learning to control a panic attack is a skill that improves with practice and needs to be worked on at home. However, panic attacks (and other withdrawal symptoms) have a knack of coming on at inappropriate moments away from home. In such circumstances it is important to stand your ground, resisting the impulse to run away. Dr Peter Tyrer suggests the following manoeuvre when a severe withdrawal symptom such as a panic attack comes on when you are pushing a trolley round a supermarket:

> "Take much slower and deeper breaths, making sure that you get air deep down into the lungs instead of just at the top of the chest."
>
> "As you do this you will find that your arms and hands relax so that the whites of your knuckles no longer show as you grip the supermarket trolley."
>
> "Do not move on until you feel the tension flowing out of your hands. With each deep breath you should feel your tension flowing away and, as it does, your symptoms will lessen or disappear."
>
> *Peter Tyrer, How to Stop Taking Tranquillisers, Sheldon Press, London 1986, p.63.*

The discovery that a panic attack can be controlled without resorting to a tablet is a great boost to self-confidence, and the development of new stress-coping strategies is often the key to successful benzodiazepine withdrawal. Panic attacks usually disappear within six weeks of withdrawal.

Generalised anxiety, panics and phobias. There are many non-pharmacological techniques for helping people with anxiety. Some of these are listed below, but it is beyond the scope of this booklet to give details of each technique or to mention all of them. None of them are essential for everybody coming off tranquillisers, but can be helpful for those having difficulty.

(1) Psychological techniques

Behaviour therapy

- aims to replace anxiety-related behaviours with better adapted behaviours
- Progressive muscular relaxation (reduces muscle tension and anxiety)
- Diaphragmatic breathing (many anxious people hyperventilate)
- Guided imaging (focus on pleasant, relaxing situations; relaxation tapes with music and calm words can also be used at home)
- Controlled exposure to frightening situations, gradually increasing till anxiety diminishes

Cognitive-behavioural therapy

- Teaches patients to understand their thinking patterns so that they can react differently to anxiety-provoking situations
- Coping skills therapy/anxiety management (learning techniques) to avoid anxiety-provoking situations and to deal with anxiety (if it occurs)
- Cognitive retraining skills

(2) Complementary medicine techniques

- Acupuncture
- Aromatherapy
- Massage, reflexology
- Homeopathy

(3) Exercise and other techniques

- Sports - aerobics, jogging, swimming, "pilates", walking and anything active that you find enjoyable
- Yoga - Many different types and techniques
- Meditation - Many different types and techniques

The choice of, and response to, each of these measures depends very much on the individual. The various psychological techniques have been formally tested and give the best long-term results. However, the outcome depends largely on the skill of the therapist, including his/her knowledge of benzodiazepines, and the rapport between therapist and client.

Of the complementary medicine techniques, all can help with relaxation during the procedure but the effects tend to be short-lived. For example, patients in my clinic who underwent a course of 12 acupuncture sessions by an acupuncturist trained in both Chinese and Western acupuncture enjoyed and felt relaxed by the sessions but they did not do any better in the long run than others who did not have acupuncture.

Certain individuals respond very well to yoga and meditation techniques. One particular patient who was confined to a wheelchair with a spastic paralysis and who was also blind, was able to come off all his benzodiazepines with the help of a meditation technique. His spasticity actually improved. However, not everyone is able to devote the mental and physical concentration required for these techniques. Physical exercise, within your own limitations, is good for everyone.

On the whole, different approaches suit different individuals and need to be personalised. If you believe in a certain approach, it will probably do you good.

Sensory hypersensitivity. A characteristic feature of benzodiazepine withdrawal is a heightened sensitivity to all sensations - hearing, sight, touch, taste and smell. When extreme, these sensations can be disturbing. One lady had to stop all the clocks in the house because their ticking sounded unbearably loud; many have had to don dark glasses because ordinary light seemed dazzlingly bright. Some find that the skin and scalp becomes so sensitive that it feels as if insects are crawling over them. Heartbeats become audible and there may be a hissing or ringing sound in the ears (tinnitus - see below). Many people complain of a metallic taste in the mouth and several notice strange, unpleasant, smells which seem to emanate from the body. These sensations, including an unpleasant smell (which usually no-one else can detect) have been described in anxiety states in the absence of benzodiazepines. Like insomnia and panics, they are probably reflections of heightened activity in the central nervous system. Such hypervigilance is part of the normal fear and flight response which is damped down by benzodiazepines but undergoes a rebound during withdrawal.

These sensations return towards normal as withdrawal progresses, and some people are pleased with the new, seemingly extraordinary, clarity of their perceptions. Only in withdrawal do they realise how much their senses have been obscured by benzodiazepines. One lady described how thrilled she was when she could suddenly see individual blades of grass in her newly bright green lawn; it was like the lifting of a veil. Thus, these sensations need not give rise to fear; they can be viewed as signs of recovery.

Depersonalisation, derealisation. Feelings of depersonalisation and of unreality are associated with benzodiazepine withdrawal, although they also occur in anxiety states. They occur most often during over-rapid withdrawal from potent benzodiazepines and are, anecdotally, particularly marked on withdrawal from clonazepam (Klonopin). In these states, the person seems detached from his body and seems almost to be observing it from the outside. Similar experiences are described in near-death states when the individual feels that he is hovering above his body, detached from the events occurring below. They are also described by people involved in extreme emergencies and in individuals subjected to torture. They are clearly not specific to benzodiazepines.

Such experiences probably represent a normal defensive reaction evolved as a protection against intolerable suffering. They may involve a primitive brain mechanism similar to the "freezing" of some animals when presented with an inescapable danger. Like other benzodiazepine withdrawal symptoms, these feelings resolve in time and should not be interpreted as abnormal or crazy.

Hallucinations, illusions, perceptual distortions. The benzodiazepine withdrawal symptom that raises most fear of going mad is hallucination. Terrifying hallucinations have occurred in people undergoing rapid or abrupt withdrawal from high doses, but the reader can be reassured that they are exceedingly rare with slow dosage tapering as outlined in Chapter II. If hallucinations occur, they are usually visual - patients have described hallucinations of a large bat sitting on the shoulder, or the appearance of horns sprouting from a human head - but auditory, olfactory and tactile hallucinations can also occur. Somewhat less frightening are hallucinations of small creatures, usually insects, which may be associated with the sensations of insects crawling on the skin (similar hallucinations occur in cocaine and amphetamine withdrawal). Sometimes hallucinations merge with illusions and misperceptions. For example, a coat hanging on the door may give the illusion of being a person. Floors apparently tilting and walls that seem to slope inwards are perceptual distortions.

The mechanisms of these bizarre symptoms are probably similar to those which cause delirium tremens (hallucinations, classically of pink elephants or rats, in the "DTs" of alcohol withdrawal). As mentioned in Chapter I, benzodiazepines cause profound perturbations throughout the brain, and abrupt withdrawal may be accompanied by uncontrolled release of dopamine, serotonin and other neurotransmitters which cause hallucinations in psychotic disorders as well as in alcohol withdrawal and cocaine, amphetamine and LSD abuse.

Once the hallucinations, which seem real at the time, are recognised as "merely" hallucinations, they quickly become less alarming. They do not herald the onset of madness; they are simply instances of benzodiazepines playing tricks on the brain which will right itself in time. A good mentor can usually reassure and "talk down" a person suffering from benzodiazepine withdrawal-induced hallucinations. In any case they should not worry anyone undergoing slow withdrawal.

Depression, aggression, obsessions. Depressive symptoms are common both during long-term benzodiazepine use and in withdrawal. It is not surprising that some patients feel depressed considering the amalgam of other psychological and physical symptoms that may assail them. Sometimes the depression becomes severe enough to qualify as a "major depressive disorder", to use the psychiatric term. This disorder includes the risk of suicide and may require treatment with psychotherapy and/or antidepressant drugs.

Severe depression may result from biochemical changes in the brain induced by benzodiazepines. Benzodiazepines are known to decrease the activity of serotonin and norepinephrine (noradrenaline), neurotransmitters believed to be closely involved in depression. Antidepressant drugs including the selective serotonin reuptake inhibitors (SSRIs such as Prozac) are thought to act by increasing the activity of such neurotransmitters.

Depression in withdrawal may become protracted (see section on protracted symptoms) and if it does not lift within a few weeks and is unresponsive to simple reassurance and encouragement, it is worth seeking a medical opinion and possibly taking an antidepressant drug (see section on adjuvant medication). Depression in withdrawal responds to antidepressant drugs in the same way as depressive disorders where benzodiazepines are not involved. If, as in many cases, an antidepressant drug is already being taken along with the benzodiazepine, it is important to continue the antidepressant until after benzodiazepine withdrawal is complete. Withdrawal from the antidepressant can be considered separately at a later stage (See Chapter II, Schedule 13).

Aggressive disorders are also associated with low serotonin activity (among other factors) and the appearance of anger and irritability during benzodiazepine withdrawal may involve similar mechanisms as depression. However, these symptoms usually disappear spontaneously and do not last very long. Obsessive disorders (Obsessive Compulsive Disorder, OCD) also respond to SSRIs, suggesting a similar mechanism. Obsessive traits may be temporarily increased during withdrawal and seem to reflect a mixture of anxiety and depression. These tend to settle spontaneously as anxiety levels decline.

Muscle symptoms. Benzodiazepines are efficient muscle relaxants and are used clinically for spastic conditions ranging from spinal cord disease or injury to the excruciating muscle spasms of tetanus or rabies. It is therefore not surprising that their discontinuation after long-term use is associated with a rebound increase in muscle tension. This rebound accounts for many of the symptoms observed in benzodiazepine withdrawal. Muscle stiffness affecting the limbs, back, neck and jaw are commonly reported, and the constant muscle tension probably accounts for the muscle pains which have a similar distribution. Headaches are usually of the "tension headache" type, due to contraction of muscles at the back of the neck, scalp and forehead - often described as a "tight band around the head". Pain in the jaw and teeth is probably due to involuntary jaw clenching, which often occurs unconsciously during sleep.

At the same time, the nerves to the muscles are hyperexcitable, leading to tremor, tics, jerks, spasm and twitching, and jumping at the smallest stimulus. All this constant activity contributes to a feeling of fatigue and weakness ("jelly-legs"). In addition, the muscles, especially the small muscles of the eye, are not well co-ordinated, which may lead to blurred or double vision or even eyelid spasms (blepharospasm).

None of these symptoms is harmful, and they need not be a cause of worry once they are understood. The muscle pain and stiffness is actually little different from what is regarded as normal after an unaccustomed bout of exercise, and would be positively expected, even by a well-trained athlete, after running a marathon.
There are many measures that will alleviate these symptoms, such as muscle stretching exercises as taught in most gyms, moderate exercise, hot baths, massage and general relaxation exercises. Such measures may give only temporary relief at first, but if practised regularly can speed the recovery of normal muscle tone - which will eventually occur spontaneously.

Bodily sensations. All sorts of strange tinglings, pins and needles, patches of numbness, feelings of electric shocks, sensations of hot and cold, itching, and deep burning pain are not uncommon during benzodiazepine withdrawal. It is difficult to give an exact explanation for these sensations but, like motor nerves, the sensory nerves, along with their connections in the spinal cord and brain, become hyperexcitable during withdrawal. It is possible that sensory receptors in skin and muscle, and in the tissue sheaths around bones, may fire off impulses chaotically in response to stimuli that do not normally affect them.

In my clinic, nerve conduction studies in patients with such symptoms revealed nothing abnormal - for example, there was no evidence of peripheral neuritis. However, the symptoms were sometimes enough to puzzle neurologists. Three patients with a combination of numbness, muscle spasms and double vision were diagnosed as having multiple sclerosis. This diagnosis, and all the symptoms, disappeared soon after the patients stopped their benzodiazepines.

Thus these sensory symptoms, though disconcerting, are usually nothing to worry about. Very occasionally, they may persist (see section on protracted symptoms). Meanwhile, the same measures suggested under muscle symptoms (above) can do much to alleviate them, and they usually disappear after withdrawal.

Heart and lungs. Palpitations, pounding heart, rapid pulse, flushing, sweating, and breathlessness are usual accompaniments of panic attacks, but may occur without panics. They do not signify heart or lung disease but are simply the expression of an overactive autonomic nervous system. Slow deep breathing and relaxation, as described under panic attacks, can do much to control these symptoms. Do not worry about them: they would be accepted as normal if you were running for a bus, and will do no more harm than if you really were!

Problems with balance. Some people during benzodiazepine withdrawal report feeling unsteady on their feet; sometimes they feel they are being pushed to one side or feel giddy, as if things were going round and round. An important organ in controlling motor stability and maintaining equilibrium is a part of the brain called the cerebellum. This organ is densely packed with GABA and benzodiazepine receptors (See Chapter I) and is a prime site of action of benzodiazepines. Excessive doses of benzodiazepines, like alcohol, cause unsteadiness of gait, slurred speech and general incoordination, including inability to walk in a straight line. It may take some time for the cerebellar systems to restabilise after benzodiazepine withdrawal and the symptoms can last until this process is complete. Exercises, such as standing on one leg, first with eyes open, then with eyes closed, can speed recovery.

Digestive problems. Some people have no problems at all with their digestive systems during or after withdrawal, and may even notice that they are enjoying their food more. Others, perhaps more prone constitutionally, may complain of a range of symptoms associated with "irritable bowel syndrome" (IBS). These can include nausea, vomiting, diarrhoea, constipation, abdominal pain, flatulence, gaseous distension and heartburn. Quite a few have found these symptoms so uncomfortable that they have undergone hospital gastrointestinal investigations, but usually no abnormality is found. The symptoms may be partly due to overactivity in the autonomic nervous system, which controls the motility and secretions of the gut and is very reactive to stress, including the stress of benzodiazepine withdrawal. In addition, there are benzodiazepine receptors in the gut. It is not clear what the functions of these receptors are or how they are affected by benzodiazepines or benzodiazepine withdrawal, but alterations in these receptors may play some part in increasing gut irritability.

Considerable loss of weight (8-10lb or more) sometimes occurs in withdrawal. This may be due to a rebound effect on appetite, since benzodiazepines have been shown to increase appetite in animals. On the other hand, some people gain weight in withdrawal. In any case, weight changes are not severe enough to worry about and normal weight is soon regained after withdrawal. A few people have difficulty in swallowing food - the throat seems to tighten up especially if eating in company. This is usually a sign of anxiety and is well-known in anxiety states. Practising relaxation, eating alone, taking small well chewed mouthfuls with sips of liquid and not hurrying make things easier and the symptom settles as anxiety levels decline.

Most digestive symptoms get better after withdrawal but in a few people they persist and become a protracted symptom, raising fears of food allergy or candida infection. These questions are discussed further in the section on protracted symptoms.

Immune system. "Why do I get so many infections?" This question is commonly asked by patients withdrawing from benzodiazepines. They seem to be prone to colds, sinusitis, ear infections, cystitis, oral and vaginal thrush (candida), other fungal infections of the skin and nails, cracked lips, mouth ulcers and influenza. Also common are complaints of adverse reactions to antibiotics used to treat some of the bacterial infections.

It is not clear whether there really is an increased incidence of infections in people undergoing benzodiazepine withdrawal, because there have been no comparisons with otherwise similar populations who have not been exposed to benzodiazepines. However, many factors affect the immune system. One of these is stress, with increased output of the stress hormone, cortisol, which inhibits immune responses. Another factor is depression, also related to stress and associated with increased cortisol secretion. Increased cortisol levels can reduce resistance to infection and also cause flare-ups of incipient infection. Benzodiazepine withdrawal can clearly be stressful but, strangely, in patients that I have tested, blood cortisol concentrations have been low. So this subject remains a mystery and probably merits further research. The message for people undergoing benzodiazepine withdrawal is to try to lead a healthy lifestyle, which includes a balanced diet, plenty of exercise and rest, and avoidance of extra stress where possible. Slow dosage tapering (Chapter II) is the best way to reduce the stress of withdrawal.

Endocrine problems. Benzodiazepines undoubtedly have effects on the endocrine system, but these have not been closely studied in humans, either during long-term benzodiazepine use or in withdrawal. Many women complain of menstrual problems but these are common in the general population and there is no clear evidence that they are directly attributable to benzodiazepines. A proportion of female long-term benzodiazepine users have had hysterectomies, but again there is no evidence of a direct link with benzodiazepine use. Occasionally both men and women on benzodiazepines complain of breast swelling or engorgement and it is possible that benzodiazepines affect secretion of the hormone prolactin. Endocrine symptoms that are due to benzodiazepines improve after withdrawal.

Fits, convulsions. Benzodiazepines are potent anticonvulsants. They can be life-saving in status epilepticus (repeated fits, one after another) and in fits caused by overdose of certain drugs (for example, tricyclic antidepressants). However, rapid withdrawal, especially from high potency benzodiazepines, can precipitate epileptic fits as a rebound reaction. Such an occurrence is extremely rare with slowly eliminated benzodiazepines (e.g. diazepam) or with slow dosage tapering. If a fit does occur in these circumstances, it is usually only a single fit and causes no lasting damage. Other phenomena seen in rapid withdrawal are psychotic symptoms, severe confusion and delirium, but again these hardly ever occur with slow dosage tapering. By following the withdrawal schedules outlined in Chapter II, you can be confident of avoiding these complications.

EXTRA MEDICATION DURING BENZODIAZEPINE WITHDRAWAL

"Is there any medication I can take to help me through withdrawal?" This question is sometimes asked by people embarking on a benzodiazepine tapering program. In contrast, others are so against drugs when they decide on withdrawal that they are loth to take anything, even the simplest pain killer. The answer to the first question is that there is no medication which will substitute for a benzodiazepine, unless it is another benzodiazepine, or a drug with benzodiazepine-like properties (such as barbiturates or zolpidem [Ambien]). All such drugs should be avoided as they only substitute one type of dependence for another. (There is a

method, advocated by some US doctors, in which phenobarbitone, a long-acting barbiturate, is substituted for a benzodiazepine and then slowly withdrawn, but this method has no particular advantages over tapering directly from a long-acting benzodiazepine).

However, there are some drugs which may help to control particular symptoms in withdrawal and which deserve consideration in certain situations though not recommended for routine use. Usually they will only be required temporarily, but they can sometimes ease a difficult situation and enable the user to proceed with the withdrawal program.

Antidepressants. Antidepressants are the most important adjuvant drugs to consider in withdrawal. As mentioned before, depression can be a real problem in withdrawal and can sometimes be severe enough to pose a risk of suicide, though this is unusual with slow tapering. Like any other depression, the depression in withdrawal responds to antidepressant drugs and is probably caused by the same chemical changes in the brain. Both the "old fashioned" tricyclic antidepressants (doxepin [Sinequan], amitriptyline [Elavil]) and the selective serotonin reuptake inhibitors (SSRIs; fluoxetine [Prozac], paroxetine [Paxil]) can be effective and an antidepressant drug may be indicated if depression is severe. There is a school of thought, mainly amongst ex-tranquilliser users, that is opposed to the taking of any other drugs during withdrawal. But suicides have occurred in several reported clinical trials of benzodiazepine withdrawal. If depression is severe during benzodiazepine withdrawal as in any other situation, it seems foolhardy to leave it untreated.

There are, however, some disadvantages with antidepressants. One is that they take 2-3 weeks or more to become really effective. This means that the patient, and his/her mentor, must be on the look-out for depression so that treatment, if advised by the doctor, can start early. The second drawback is that anxiety may be temporarily worsened at the start of treatment either with tricyclics or SSRIs. This is a particular risk during benzodiazepine withdrawal when anxiety levels are usually high. To avoid aggravation of anxiety, it is important to start with the lowest possible dose of an antidepressant and then work up slowly, over two or three weeks. Do not be persuaded by your doctor to start immediately on the "therapeutic" dose for depression. There are also fears that antidepressants such as Prozac may in some patients induce an agitated, violent or suicidal state at the start of treatment; low initial dosage and careful monitoring may avoid this risk.

It is usually possible to continue with slow benzodiazepine tapering while starting on an antidepressant, although some may prefer to halt their programme for 2-3 weeks until the antidepressant has "taken hold" (but increasing the benzodiazepine dose should be strenuously avoided). Antidepressants not only alleviate depression but also, after 2-3 weeks, have anti-anxiety effects. They are in fact a better long-term treatment than benzodiazepines for anxiety, panic and phobic disorders, and may in some cases actively help the benzodiazepine withdrawal process.

Once started on an antidepressant for depression, the treatment should be continued for some months (usually about 6 months) to avoid recurrence of the depression. Benzodiazepine tapering can continue during this time, and the antidepressant will sometimes act as a welcome umbrella during the last stages of withdrawal. It is important to finish the benzodiazepine withdrawal before starting to withdraw the antidepressant. Quite often, people taking long-term benzodiazepines are already taking an antidepressant as well. In this case they should stay on the antidepressant until the benzodiazepine withdrawal is complete.

Another drawback of antidepressants is that they, too, cause withdrawal reactions if they are stopped suddenly, a fact which has not always been appreciated by doctors. Antidepressant withdrawal symptoms include increased anxiety, sleep difficulties, influenza-like symptoms, gastrointestinal symptoms, irritability and tearfulness - not much different, in fact, from benzodiazepine withdrawal symptoms. These reactions can be prevented by slow tapering of the antidepressant dosage over about 1-3 months (See Table 2). Most people who have withdrawn from benzodiazepines will be experts at tapering dosages when the time comes to stop the antidepressant and will be able to work out a rate of withdrawal that suits them.

Apart from their therapeutic effects in depression and anxiety, some antidepressants have a sedative effect which patients who are particularly plagued with insomnia have found helpful. Low doses (10-50mg) of amitriptyline (Elavil) or doxepin (Sinequan) are remarkably effective in promoting sleep if taken at bed-time. These can be taken for short periods of a few weeks and stopped by reducing the dosage stepwise or taking the drug every other night. Withdrawal is not a problem when small doses are taken for short periods or intermittently.

TABLE 2. ANTIDEPRESSANT WITHDRAWAL SYMPTOMS

PHYSICAL SYMPTOMS

Gastrointestinal: abdominal pain, diarrhoea, nausea, vomiting
Influenza-like: fatigue, headache, muscle pain, weakness, sweating, chills, palpitations
Sleep disturbance: insomnia, vivid dreams, nightmares
Sensory disturbances: dizziness, light-headedness, vertigo,
pins and needles, electric shock sensations
Motor disorders: tremor, loss of balance, muscle stiffness, abnormal movements

PSYCHOLOGICAL SYMPTOMS

Anxiety, agitation
Crying spells
Irritability
Overactivity
Aggression
Depersonalisation
Memory Problems
Confusion
Lowered mood

Beta-blockers. In a few cases, severe palpitations, muscle tremors or motor jerks develop during benzodiazepine withdrawal and hinder progress. These symptoms can be controlled or ameliorated by beta-blocking drugs such as propranolol (Inderal). Drugs of this type inhibit the effects of excess epinephrine and norepinephrine (adrenaline and noradrenaline) released by an overactive sympathetic nervous system. They slow the heart and prevent excess muscle activity. Although they have little effect on psychological symptoms, they can cut the vicious circle in which palpitations or tremor create anxiety which leads to yet more palpitations. Some people in benzodiazepine withdrawal take small doses of these drugs (10-20mg Inderal three times daily) regularly, while others reserve them to take only if the physical symptoms of a panic attack seem uncontrollable. They are not a cure, but can sometimes help people through a difficult situation. In larger doses, beta-blockers are used for raised blood pressure and angina, but such doses are not advised in benzodiazepine withdrawal. They should not be taken by anyone who has asthma as they can cause constriction of the bronchial tubes. If beta-blockers have been used regularly for any length of time, they should be withdrawn slowly by tapering the dosage, as they too can cause a withdrawal reaction of increased heart rate and palpitations.

Hypnotics and sedatives. Most other hypnotics and sedatives act in a similar way to benzodiazepines, including barbiturates, chloral derivatives (Noctec), ethchlorvynol (Placidyl), zopiclone (Zimovane, Imovane), zolpidem (Ambien), zaleplon (Sonata) and, incidentally, alcohol. None of these drugs should be used as alternative sleeping pills or sleeping draughts during benzodiazepine withdrawal. All can cause a similar type of dependence and some are more toxic than benzodiazepines.

If sleep is really a problem, a small dose of a tricyclic antidepressant with sedative effects (see antidepressants, above) is a possible option. Alternatively, an antihistamine with sedative effects (e.g. diphenylhydramine [Benadryl], promethazine [Phenergan]) may be used temporarily. Neither antidepressants nor antihistamines act by the same mechanisms as benzodiazepines.

Some drugs related to major tranquillisers have sedative effects and are also used for nausea, vertigo and motion sickness. These are sometimes prescribed during withdrawal, especially prochlorperazine (Compazine). However, such drugs can have serious side effects (motor disorders like Parkinson's disease) and are not recommended for long-term use or as a substitute for benzodiazepines.

Other drugs. Several other drugs have been tested in clinical trials of benzodiazepine withdrawal to see if they could speed the process, prevent or alleviate withdrawal symptoms, or improve the long-term success rate. Many of these trials have involved what is considered here as over-rapid withdrawal. For example, a recent US study of benzodiazepine withdrawal in long-term users (Rickels, Schweizer et al. Psychopharmacology 141,1-5,1999) tested the effects of a sedative antidepressant (trazodone, Desyrel) and an anticonvulsant drug (sodium valproate, Depakote). Neither drug had any effect on the severity of withdrawal symptoms, but the rate of taper was 25% of the benzodiazepine dose each week - a rather fast withdrawal! Other drugs

which have been found to be of little or no value in withdrawal trials over 4-6 weeks include buspirone (BuSpar, an anti-anxiety drug), carbamazepine (Tegretol, an anticonvulsant), clonidine (Catapres, an anti-anxiety drug sometimes used in alcohol detoxification), nifedipine (Adalat) and alpidem.

There have been some reports that gabapentin (Neurontin), tiagabine (Gabitril) and possibly pregabalin (yet to be licensed) help with sleep and anxiety in withdrawal. However, there have been no controlled trials and it is not clear whether these drugs themselves cause withdrawal effects. In practice additional drugs are seldom needed with very slow benzodiazepine tapering. Only in special situations there might be a place for an antidepressant, beta blocker, sedative antihistamine or anticonvulsant. There is no need to avoid ordinary pain killers such as Tylenol, Feldene etc. for everyday aches and pains.

BENZODIAZEPINE USE DURING AND AFTER WITHDRAWAL

What happens if someone who is in the course of benzodiazepine withdrawal or has successfully withdrawn needs a surgical operation? Benzodiazepines are of value as premedication before major operations and for sedation and amnesia during minor surgical procedures. Yet many ex-users are terrified that if they are given a benzodiazepine for these purposes they will become dependent all over again. They can be reassured: a single dose of a benzodiazepine given for an operation does not bring back the addiction, although the stress of an operation may re-awaken the anxiety symptoms experienced during benzodiazepine withdrawal. Symptoms reported under these circumstances have usually been the result of fear. Many personally observed patients have had repeated doses of midazolam (Versed, Hypnovel), a short-acting benzodiazepine, for dental procedures (dental phobia is common in withdrawal), and other benzodiazepines including diazepam for major and minor surgery and have recovered without complications.

Also, people who have gone back on benzodiazepines, having failed at the first attempt at withdrawal, can be just as successful at tapering as first-timers.

DIET, FLUIDS AND EXERCISE

There has been increasing interest in the question of diet in benzodiazepine withdrawal, particularly in North America. What food/drinks should be excluded? What supplements should be added? These are frequent questions. In my opinion there is no need to be over-obsessive about diet. Some people advise that caffeine and alcohol should be completely ruled out. However, the point about gradual dosage tapering at home is that people should get used to living a normal lifestyle without drugs. In my experience, coffee or tea in moderation (about two cups a day), or reasonable amounts of cocoa, chocolate or coca cola, are perfectly compatible

with benzodiazepine withdrawal - except in the few individuals who are exquisitely sensitive to caffeine or those with very high anxiety levels. Clearly one should not take caffeine late in the evening or drink cups of tea/coffee (unless decaffeinated) in the middle of the night if insomniac, but to prohibit a cup of tea/coffee at breakfast is in general unduly restrictive. One is, after all, striving to be normal and sociable, not fussy.

Similarly with alcohol: a glass or two of wine is perfectly permissible (and even said by some to be advisable for health). Although it is important not to substitute increasing doses of alcohol for decreasing doses of benzodiazepines, there is no need to deny oneself small pleasures. Moderation is the key: there is no call to be puritanical.

The same principles apply to food. Humans are singularly well adapted through evolution to obtain the nutrients they need from a wide variety of diets and to eliminate unwanted products. A normal healthy diet which includes generous amounts of fruit and vegetables and a source of protein and fats (from meat or vegetables), and not too much pure sugar or "junk foods", provides all the nutrients a person needs. There is no general need for dietary supplements or extra vitamins or minerals or for "detoxifying" measures. All these can be harmful in excess. Advice to cut out white flour, white sugar etc. may help certain individuals but I have also observed that overly restrictive diets can have adverse effects. Some people say they have felt much better after going on a particular diet - this makes one wonder what sort of diet they were eating before!

Individuals may find they are intolerant of certain foods although this is not usually a true allergy. In this case, let common sense prevail and avoid such foods for a while. If in doubt, get the advice of a reliable and unbiased nutritionist, but in general stick to a normal healthy diet without food fads. Before diets became "fashionable" thousands of people successfully came off their benzodiazepines in many different countries with widely varying dietary habits without restriction - and this continues today.

A normal diet includes a normal amount of fluid consumption. Requirements for water and salt vary with body size, environmental temperature, amount of exercise, etc. so cannot be stated categorically. However, there is no need to drink extra amounts of fluid during withdrawal with the idea of "flushing out impurities/toxins". The body is very good at doing this, even at minimal fluid consumption, and surplus water is simply excreted.

Regular moderate exercise is recommended during withdrawal as it maintains general fitness, builds up stamina, increases the circulation to brain, muscle and skin and improves mood, but there is no point in slavishly doing exercises that you hate. The aim is to lead a healthy lifestyle which by definition includes some exercise in a form that is enjoyable for you.

Smoking. I hardly dare to mention smoking in view of present day attitudes to this unfortunate addiction, but for those who are smokers it is probably asking too much to attempt to stop smoking and withdraw benzodiazepines at the same time. Many people have found that giving up smoking is easier when they are off benzodiazepines, when the desire for nicotine may even

wane somewhat. In general, excessive worrying over your undesirable habits (or your diet) can add to the stress of withdrawal. It is better to relax a bit and be gentle with yourself.

COURSE OF WITHDRAWAL

During benzodiazepine withdrawal, symptoms characteristically wax and wane, varying in severity and type from day to day, week to week, and even during the course of a day. Some symptoms come and go; others may take their place. There is no need to be discouraged by these wave-like recurrences; the waves become less severe and less frequent as time passes. Typically "Windows" of normality, when you feel positively well for a few hours or days, appear after some weeks; gradually the "Windows" become more frequent and last longer, while any intervening discomfort ebbs away.

It is impossible to give an exact time for the duration of withdrawal symptoms. It depends on where you start from, how much support you need and receive, how you manage your taper and many other factors. With slow tapering, some long-term users have virtually lost all their symptoms by the time they take their last tablet, and in the majority symptoms disappear within a few months. Vulnerability to extra stress may last somewhat longer and a severe stress may - temporarily - bring back some symptoms. Whatever your symptoms, it is best not to dwell on them. Symptoms are just symptoms after all and most of them in withdrawal are not signs of illness but signals of recovery. Furthermore, as your mind clears, you can work out more and more effective ways to deal with them so that they become less significant.

One reassuring finding from many clinical studies is that eventual success in withdrawal is not affected by duration of use, dosage or type of benzodiazepine, rate of withdrawal, severity of symptoms, psychiatric diagnosis, or previous attempts at withdrawal. Thus from almost any starting point, the motivated long-term user can proceed in good heart.

PROTRACTED WITHDRAWAL SYMPTOMS

A minority of people who have withdrawn from benzodiazepines seem to suffer long-term effects - protracted symptoms that just don't go away after months or even years. It has been estimated that perhaps 10-15 per cent of long-term benzodiazepine users develop a "post-withdrawal syndrome". Many of these people have taken benzodiazepines for 20 years or more and/or have had bad experiences in withdrawal. The incidence of protracted symptoms in those who have undergone a slow taper under their own control is almost certainly very much lower.

Table 3 shows the symptoms most likely to be long-lasting. These include anxiety, insomnia, depression, various sensory and motor symptoms, gastrointestinal disturbances, and poor memory and cognition. The reasons why these symptoms persist in some people are not clear. Probably many factors are involved, some directly due to the drug and some to indirect or secondary effects (See Table 4).

TABLE 3. SOME PROTRACTED BENZODIAZEPINE WITHDRAWAL SYMPTOMS

Symptoms	Usual Course
Anxiety	- Gradually diminishing over a year
Depression	- May last a few months; responds to antidepressant drugs
Insomnia	- Gradually diminishing over 6-12 months
Sensory symptoms: tinnitus, tingling, numbness, deep or burning pain in limbs, feeling of inner trembling or vibration, strange skin sensations	- Gradually receding but may last at least a year and occasionally several years
Motor symptoms: muscle pain, weakness, painful cramps, tremor, jerks, spasms, shaking attacks	- Gradually receding but may last at least a year and occasionally several years
Poor memory and cognition	- Gradually receding but may last at least a year and occasionally several years
Gastrointestinal symptoms	- Gradually improving but may last a year and occasionally several years

TABLE 4. SOME POSSIBLE CAUSES OF PROTRACTED BENZODIAZEPINE WITHDRAWAL SYMPTOMS

Possible mechanisms	Effects
1. Learning of stress-coping strategies blocked by benzodiazepine use exposed on withdrawal	Anxiety, vulnerability to stress
2. Impairment of memory caused by benzodiazepines prevents normal resolution of distressing life events which are exposed on withdrawal	Anxiety, depression

3. Traumatic experiences during previous withdrawal	Post-traumatic stress symptoms
4. (?) Biochemical alterations caused by benzodiazepines (serotonin, norepinephrine [noradrenaline], stress hormones)	Depression
5. Nervous system hyperexcitability due to persisting changes in GABA/ benzodiazepine receptors	Sensory and motor symptoms, anxiety, insomnia
6. (?) Structural or functional damage to brain tissue	Poor memory and cognition
7. (?) Changes in gut and immune systems	Gastrointestinal symptoms
8. (?) Long-term retention of benzodiazepines in tissues of the body	Prolongs nervous system hyperexcitability

(?) indicates possible mechanisms for which at present there is no scientific evidence

Anxiety. Anxiety persisting after the acute phase of withdrawal may be partly due to the uncovering of a learning defect caused by the benzodiazepines. These drugs specifically impair the learning of new skills, including stress-coping strategies. Such skills are normally acquired continuously from childhood to middle age or later as experience of life accumulates. Their development may be blocked for a period of years during which benzodiazepines are taken. After withdrawal the ex-user is left in a vulnerable state with a decreased ability to deal with stressful situations. Full recovery may require many months of learning new stress-coping strategies to replace the years when this facility was blanketed by pills.

Secondly, benzodiazepine withdrawal may uncover life problems that have never been fully addressed. For example, the impairment of memory caused by benzodiazepines may prevent the normal resolution of personal stresses such as bereavement or a car crash. Such buried or half-forgotten experiences may have to be faced after withdrawal and may prolong both anxiety and depression. It is not uncommon for a widow or widower, first prescribed benzodiazepines on the death of the spouse, to go through the grieving process for the first time after withdrawal, even though the bereavement had occurred many years previously.
A third factor may operate in people who have had frightening experiences during withdrawal. This is not uncommon in those who have undergone rapid withdrawal without adequate explanation, often in hospital or detoxification centres but sometimes at home when their doctor has withdrawn prescriptions. Such people may develop symptoms of post-traumatic stress

disorder (PTSD) in which their experiences are constantly repeated as flashbacks or nightmares and so prolong the anxiety.

In addition, many (though by no means all) long-term benzodiazepine users are constitutionally highly strung, sensitive people with relatively low self-esteem, whose anxiety problems have led to the prescription of benzodiazepines in the first place and whose continuing anxiety (possibly heightened by the benzodiazepines) has prompted the doctor to go on prescribing the drugs. It may take a long time for these people to regain, or attain, full confidence in themselves.

Despite these factors, protracted anxiety symptoms, including agoraphobia and panics, do tend to subside gradually and rarely last more than a year. The process may be hastened by good psychological support and by the measures described under acute anxiety symptoms. Believe it or not, people often feel more self-confident after withdrawal than they did before starting to take benzodiazepines.

Depression. Depression may be caused or aggravated by chronic benzodiazepine use, but is also a feature of the withdrawal syndrome. Depressive symptoms may appear for the first time after withdrawal, sometimes after a delay of a few weeks, and it can be severe and protracted for some months. It is not clear whether people who have had depression before, or have a family history of depression, are more prone to this complication, and its causes are not understood. As discussed in Chapters I and II, benzodiazepines disrupt the function of many neurotransmitters and hormones and depression could be the result, for example, of low serotonin activity combined with the stress of withdrawal. If severe enough to require definitive treatment, the depression in withdrawal responds to antidepressant drugs and/or cognitive therapy and usually diminishes gradually over 6-12 months.

Insomnia. Poor sleep is a common accompaniment of both anxiety and depression. In anxiety there is typically a difficulty in falling asleep, while depression is associated with early morning waking as well as frequent wakings during the night. Insomnia is also common as an acute withdrawal symptom along with nightmares and other sleep disturbances. Occasionally, however, insomnia (sometimes with "restless legs" and muscle jerks) persists as an isolated symptom after other symptoms have disappeared, and may last for many months. However, poor sleepers can be reassured that an adequate sleep pattern does return at last. There are powerful natural mechanisms in the body which ensure that the brain does not become severely sleep-deprived.

Sensory and motor disturbances. There is no doubt that benzodiazepine withdrawal leaves in its wake a nervous system that is exquisitely sensitive to all sensory and motor stimuli. Usually this state settles in a few weeks but occasionally disturbing sensations persist.

One of the most distressing sensory symptoms is **tinnitus**, a constant ringing or hissing in the ears which has been noted in several studies of benzodiazepine withdrawal. One lady described her tinnitus as a "needle of sound" piercing deep inside her head. Tinnitus is often associated

with a degree of hearing loss and is not uncommon in people with partial nerve deafness who have never taken benzodiazepines. Nevertheless, it often makes its first appearance during benzodiazepine withdrawal in people who have had hearing loss for years. Also, it may be unilateral or precisely localised, even in those with symmetrical bilateral hearing loss. Whether people who have taken long-term benzodiazepines are particularly prone to tinnitus and if so why, is not known. It can persist for years and does not always respond to the usual treatments for tinnitus (maskers, etc); nor is it always relieved by restarting benzodiazepines. However, people with persisting tinnitus after withdrawal should seek the advice of a hearing specialist and may be lucky enough to find a clinic which specialises in this symptom.

A number of unpleasant bodily sensations may persist after withdrawal including tingling, "pins and needles" or patches of numbness in the trunk, face, limbs and fingers. These may be accompanied by burning pain or aches that sometimes seem to originate deep in the muscles or bones. Some people complain of an "inner trembling" or a sense of vibration, and some have described bizarre sensations as of water or slime running over the body or a serpent-like writhing on the scalp. Motor symptoms that may persist include muscle tension, weakness, cramps, jerks, spasms and shaking attacks.

Possible mechanisms of persisting sensory and motor symptoms. Although the above symptoms are often made worse by stress, they are clearly not simply due to anxiety. They suggest a dysfunction in motor and sensory pathways in the spinal cord and/or brain. A possible clue to their mechanism is provided by a trial with flumazenil (Anexate, Romazicon) a benzodiazepine receptor antagonist, published by Lader and Morton (Journal of Psychopharmacology 1992, 6, 357-63). This drug, when infused intravenously brought rapid relief of protracted symptoms (muscle tension, "pins and needles", weakness, muscle cramps or jerks, burning, tremor or shaking) that had been present for 5-42 months post-withdrawal in 11 patients. The symptoms were improved by 27-82 percent and the greatest response occurred in patients with the lowest anxiety ratings. There was no response to infusions of saline solution.

Flumazenil is thought to act by "resetting" GABA/benzodiazepine receptors (See Chapter I) so that they are more receptive to the inhibitory actions of GABA. The results suggest that some protracted symptoms are due to the failure of the receptors to revert to their normal state after they have become unresponsive to GABA, due to the development of tolerance (See Chapter I). The response to flumazenil also shows that benzodiazepines can cause longer-lasting pharmacological effects than previously believed.

Unfortunately, flumazenil does not at present offer a practical cure for protracted symptoms. The drug has to be infused intravenously and is very short acting so that symptom relief is only temporary. The drug cannot be given to a person who is still taking benzodiazepines as it precipitates an acute withdrawal reaction. However, although protracted sensory and motor symptoms may sometimes seem to be almost permanent, they do in fact decline in severity over the years, even without flumazenil, and they do not signify a major neurological illness.

Such symptoms may be partially alleviated by relaxation techniques; some motor and sensory systems may respond to carbamazepine (Tegretol) and motor symptoms may respond to propranolol (Inderal).

Poor memory and cognition. Although it is well known that benzodiazepines impair memory and some cognitive functions, particularly the ability to sustain attention, some long-term users complain of continued loss of intellectual abilities persisting after withdrawal. There have been several studies on this question which indicate that improvement may be very slow. The longest studies in therapeutic dose long-term users extend for only 10 months after withdrawal. Cognitive impairment, though slowly improving, persisted for at least this time and was not related to anxiety levels (Tata et al. Psychological Medicine 1994, 24, 203-213). Some Swedish studies have found that intellectual impairment, although improved, was still present 4-6 years after cessation of benzodiazepine use, but it was not clear whether high dosage and/or alcohol use were added factors.

Do benzodiazepines cause structural brain damage? These results have raised the question of whether benzodiazepines can cause structural brain damage. Like alcohol, benzodiazepines are fat soluble and are taken up by the fat-containing (lipid) membranes of brain cells. It has been suggested that their use over many years could cause physical changes such as shrinkage of the cerebral cortex, as has been shown in chronic alcoholics, and that such changes may be only partially reversible after withdrawal. However, despite several computed tomography (CT) scan studies, no signs of brain atrophy have been conclusively demonstrated in therapeutic dose users, and even the results in high dose abusers are inconclusive. It is possible that benzodiazepines can cause subtle changes which are not detected by present methods, but on the available evidence there is no reason to think that any such changes would be permanent.

Gastrointestinal symptoms. Gastrointestinal symptoms may be prolonged after withdrawal, usually in people who have a previous history of digestive troubles. Such people may develop apparent intolerance to certain foods, although reliable tests for true food allergy (e.g. antibodies against specific food constituents) are nearly always negative. Nevertheless many sufferers feel that they have damage to the immune system or have developed intestinal candidiasis. There is at present no clear scientific evidence on these topics, though as mentioned before, benzodiazepine receptors are present in the gut and benzodiazepine use or withdrawal may affect immune responses. There is some evidence that chronic hyperventilation provokes the release of histamine (a substance released in allergic reactions) and that the incidence of food-intolerance and "pseudo-allergic" reactions is high in chronic hyperventilators. Advice on diet, breathing and candida infections is given in books by Shirley Trickett quoted at the end of this chapter. It is usually inadvisable to stick to a strict exclusion diet; with a normal balanced diet and sensible general health measures, including regular exercise, gastrointestinal symptoms due to withdrawal gradually abate.

Coping with protracted symptoms. A number of people are expressing fears that some benzodiazepine withdrawal symptoms last forever, and that they can never completely recover. Particular concerns have been raised about impairment of cognitive functions (such as memory and reasoning) and other lingering problems such as muscle pains and gastrointestinal disturbances.

People with such worries can be reassured. All the evidence shows that a steady decline in symptoms almost invariably continues after withdrawal, though it can take a long time - even several years in some cases. Most people experience a definite improvement over time so that symptoms gradually decrease to levels nowhere near as intense as in the early days of withdrawal, and eventually almost entirely disappear. All the studies show steady, if slow, improvement in cognitive ability and physical symptoms. Although most studies have not extended beyond a year after withdrawal, the results suggest that improvement continues beyond this time. There is absolutely no evidence that benzodiazepines cause permanent damage to the brain, nervous system or body.

People bothered by long-term symptoms can do a lot to help themselves. For example:

1. Exercise your body. Physical exercise improves the circulation and function of both brain and body. Find an exercise that you enjoy: start at low level, work up gradually and keep it up regularly. Exercise also helps depression, decreases fatigue and increases general fitness.
2. Exercise your brain. Use your brain to devise methods to improve its efficiency: make lists, do crossword puzzles, find out what bothers you most - there is always a way round it. Cognitive retraining helps people to find ways around their temporary impairment.
3. Increase your interests. Finding an outside interest which you have to work at employs the brain, increases motivation, diverts attention away from your own symptoms and may even help others.
4. Calm your emotions. Above all, stop worrying. Worry, fear and anxiety increase all withdrawal symptoms. Many of these symptoms are actually due to anxiety and not signs of brain or nervous system damage. People who fear withdrawal have more intense symptoms than those who just take it as it comes and think positively and confidently about recovery.

How long do benzodiazepines stay in the body after withdrawal? This question is often asked by people with long-term symptoms. Is it possible that one cause of protracted symptoms is that benzodiazepines remain in the body even after months, lurking perhaps deep in such tissues as brain and bones? Could slow elimination from these sites keep the withdrawal symptoms going?

Like many other issues concerning benzodiazepines, the answers to these questions are still unclear. Benzodiazepine concentrations in the blood have been measured and shown to reach

undetectable levels in 3-4 weeks after cessation of use in people withdrawn from clinical doses. Information on benzodiazepine concentrations in the brain and other tissues is difficult to obtain, especially in humans. Benzodiazepines certainly enter the brain and also dissolve in all fatty (lipid-containing) tissues including fat deposits all over the body. It is possible that they linger in such tissues for some time after blood levels have become undetectable. However, most body tissues are in equilibrium with the blood that constantly perfuses them, and there is no known mechanism whereby benzodiazepines could be "locked up" in tissues such as the brain. There is no data on how long benzodiazepines remain in bones, which have a lower fat content but also a slower rate of cell turnover.

Nevertheless, the concentration of benzodiazepines remaining in body tissues after withdrawal must be very low, otherwise the drugs would leak back into the blood in discernible amounts. It is difficult to imagine that such concentrations would be sufficient to produce clinical effects or that any direct effects could last for months or years. However, it is not inconceivable that even low concentrations might be enough to prevent the return of GABA/benzodiazepine receptors in the brain to their pre-benzodiazepine state. If so, the receptors would continue to be resistant to the natural calming actions of GABA (See Chapter I), and the effect could be to prolong the state of nervous system hyperexcitability. Possible factors contributing to protracted symptoms are outlined in Table 4.

EPILOGUE

This chapter ends with many unknowns. Benzodiazepine withdrawal remains an unfinished story and several aspects need serious attention:

1. **Education.** All doctors and paramedicals need to acquire greater knowledge and to receive better training on the prescription of benzodiazepines (short-term only), their adverse effects (especially dependence), and methods of withdrawal (slow tapering of dosage combined with adequate support). Such education should include family physicians, psychiatrists, other specialists, staff in detoxification units, pharmacists, psychologists and other therapists and community nurses. Increased general awareness and pressure from the public could speed these measures.

2. **Research.** More research is needed on the effects of long-term benzodiazepine use. Particular areas include effects on the brain structures, using modern techniques such as magnetic resonance imaging (MRI) and brain blood flow (fMRI), combined with neuropsychological testing. Further work is also needed in the little researched fields of benzodiazepine actions on endocrine, gastroenterological and immune systems.

3. **Treatment methods.** Better methods for treatment of anxiety and insomnia need to be developed. It is doubtful if any drug will ever "cure" anxiety or insomnia but it may be possible to develop pharmacological agents with fewer side-effects. For example, rats treated with the benzodiazepine antagonist flumazenil along with a benzodiazepine do

not develop tolerance but still apparently experience an anxiolytic effect. Such a combination might work in humans but long-acting benzodiazepine antagonists that can be taken by mouth have not been subjected to trials. Alternatively, mood-stabilising anticonvulsants such as gabapentin, tiagabine and pregabalin may hold promise since their mode of action is different from that of benzodiazepines. At the same time, psychological therapies for treating anxiety and insomnia could be improved and more widely taught. And it may well be possible to develop better methods than those described in this monograph for drug withdrawal in people who have become dependent on benzodiazepines.

4. **Provision of facilities.** Facilities for benzodiazepine dependent people need to be developed. Detoxification units, dealing with dependence on alcohol and illicit drugs, are not appropriate for prescribed benzodiazepine users who have unwittingly become dependent through no fault of their own. Such places usually withdraw the drugs too rapidly and apply rigid "contract" rules which are quite unsuitable for benzodiazepine patients struggling with withdrawal symptoms. Much needed are clinics specialising in benzodiazepine withdrawal where clients can receive individualised, flexible, understanding and supportive counselling. At present only too few voluntary support groups valiantly strive to fill this gap with minimal finances. Proper financing would also allow provision of residential accommodation where clients in need could go for short breaks in a supportive, non-hospital, atmosphere at crucial times during their withdrawal process.

Finally, it is a tragedy that in the 21st century millions of people worldwide are still suffering from the adverse effects of benzodiazepines. Nearly 50 years after benzodiazepines were introduced into medical practice in the 1950s there should be no need for a monograph such as this. However, I hope that the experience from many patients described in this book will help to raise awareness amongst the medical profession and the public of the problems associated with long-term benzodiazepine use and withdrawal.

FURTHER READING

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THE ASHTON MANUAL SUPPLEMENT

A Supplement to *Benzodiazepines: How They Work & How to Withdraw* (2002)

Professor C Heather Ashton, DM, FRCP
April, 7 2011
(additions 2012 & 2013)
The Ashton Manual · Professor Ashton's Main Page

Overview

There has been little clinical progress in the benzodiazepine world since 2002 when the last edition of "Benzodiazepines: How they work and how to withdraw" appeared on www.benzo.org.uk. Benzodiazepines are still over-prescribed globally, often in excessive doses and frequently for too long. Prescriptions for benzodiazepines and the similar 'Z-drugs' are actually increasing in many countries. There is a tendency to prescribe the more potent agents such as clonazepam (Klonopin) and, in the U.S. particularly, alprazolam (Xanax) and zolpidem (Ambien), while lorazepam (Ativan) is still the most commonly prescribed drug for anxiety. The availability of benzodiazepines on the internet has increased their use as 'self-medication' in the general public who are often unaware of their adverse effects and dependence potential. This availability has also added to benzodiazepine use in multidrug abusers.

Many doctors have little knowledge of, or expertise in, the management of benzodiazepine withdrawal in long-term users, and skilled psychological support is hard to obtain due to a shortage of clinical psychologists. Good advice on withdrawal is available for doctors in the UK (for example from Clinical Knowledge Summaries or the British Medical Formulary) and in the US from the Maine Benzodiazepine Study Group (MBSG) but few make use of this information. Detoxification centres which also deal with alcohol and illegal drugs are not appropriate for prescribed benzodiazepine users. Such clinics tend to withdraw patients too rapidly, apply rigid rules and 'contract' methods, and provide inadequate support or follow-up. There are no longer any dedicated hospital withdrawal clinics in the U.K. although there are a few NHS-supported charities and support groups devoted to benzodiazepine problems (see contacts list below).

Clinical research on optimal benzodiazepine withdrawal methods is limited. The results from meta-analyses of clinical trials are difficult to interpret because different trials use different rates of withdrawal, different methods of psychological support, often use different adjuvant drugs, many of which have not been tested in controlled studies of withdrawal, and allow only for short-term follow-up. There are no studies examining long-term effects of benzodiazepines such as protracted symptoms or possibly permanent effects. The question of whether benzodiazepines can cause permanent damage to the brain or other systems, as many ex-users claim, remains unanswered by science. Basic research into the molecular mechanisms underlying tolerance,

withdrawal symptoms and anxiety, and on the interactions of benzodiazepines with various neurotransmitter systems, has yielded some interesting results but these are not readily translated into clinical practice, although they may lead to future clinical advances.

The advice given to prescribed benzodiazepine users (and their doctors) in the 'Ashton Manual' remains relevant today and requires little updating. This supplement adds further information in response to questions that have frequently been asked by benzodiazepine users during and after withdrawal. Such questions are difficult to answer because, like most benzodiazepine problems, they depend on many individual factors. Such factors include personality and genetic make-up, reasons for benzodiazepine prescription, dose, duration and type of benzodiazepine use, present symptoms, environmental stresses and others. Individuals seeking answers from the general information provided in this supplement need to work out which factors apply to them personally.

The questions I have most frequently been asked about benzodiazepines are:

1. Does long-term benzodiazepine use cause permanent brain damage?
2. Why do apparent recurrences of benzodiazepine withdrawal symptoms occur, (often a long time after) successful withdrawal?
3. Should benzodiazepine treatment be reinstated if withdrawal symptoms persist after withdrawal?

I have attempted to answer these, and some related, questions in this supplement to the Manual.

Permanent brain damage?

Structural damage. Many long-term benzodiazepine users who have stopped taking the drugs complain of a variety of seemingly irreversible psychological and/or physical symptoms which they attribute to permanent brain damage caused by the drugs. However, the question of whether benzodiazepines cause brain damage is still unsolved. In 1982 Professor Malcolm Lader and colleagues reported the results of a small study using CAT (computerised axial tomography) brain scans in 14 long-term benzodiazepines users compared with control subjects. Two of the benzodiazepine users had definite cortical brain atrophy and there was a borderline abnormality in five others; the rest were normal. In a 1984 study by Professor Lader involving 20 patients, the results were again suggestive but there was no relationship between CAT scan appearances and the duration of benzodiazepine therapy. The study concluded "The clinical significance of the findings is unclear." Subsequent CAT scan studies in 1987, 1993, and 2000 failed to find any consistent abnormalities in long-term benzodiazepine users, and concluded that benzodiazepines do not cause structural brain damage, e.g death of neurones, brain shrinkage or atrophy etc. A later more accurate development in brain scanning, MRI (magnetic resonance imaging), does not appear to have been systematically studied in benzodiazepine users. However MRI, like CAT, only shows structural changes and it is unlikely

that the use of this technique would clarify the picture; many still symptomatic long-term ex-benzodiazepine users have had normal MRIs.

Functional damage. It is more likely that any long-term brain changes caused by benzodiazepines are *functional* rather than *structural*. In order to show such changes it would be necessary to examine abnormalities of brain *activity* in long-term benzodiazepine users. Techniques for such studies are available: fMRI (functional MRI) measures regional blood flow; PET (positron emission tomography) and SPECT (single photon emission tomography) measure neurotransmitter and receptor activity; QEEG (quantitative electroencephalography) and MEG (magnetoencephalography) measure regional electrical activity. None of these techniques has been utilised in controlled studies of long-term benzodiazepine users. Cognitive performance could indicate impairments in certain brain areas, but no studies have extended for more than six months. Finally *post-mortem* studies could show abnormalities in brain receptors, and animal studies could show changes in neuronal gene expression. None of these studies has been undertaken. Nor have there been any studies examining abnormalities in other tissues or organs in long-term benzodiazepine users.

A controlled study of long-term benzodiazepine users using brain function techniques would have to be carefully designed and would involve a large number of age and sex matched subjects, probably over 100 in both control and user groups. In the benzodiazepine group it would have to take into account dose, type of benzodiazepine, duration of use, psychiatric history, symptoms, use of alcohol and other drugs, and a number of other factors. Such a study would be expensive and funding would be difficult to obtain. Drug companies would be unlikely to offer support, and to date 'independent' bodies such as the Medical Research Council, the Wellcome Foundation and the Department of Health have shown little interest. Thus the question of whether benzodiazepines cause brain or other organ damage remains unanswered.

Long-term effects of benzodiazepines

One mechanism which might be involved in long-term (and possibly permanent) effects of benzodiazepines is an alteration in the activity of benzodiazepine receptors in brain GABA neurones. These receptors down-regulate (become fewer) as tolerance to benzodiazepines develop with chronic use. Such down-regulation is a homeostatic response of the body to the constant presence of the drugs. Since benzodiazepines themselves enhance the actions of GABA, extra benzodiazepine receptors are no longer needed, so many are, in effect, discarded. These down-regulated receptors are absorbed into neurones where, over time, they undergo various changes including alterations in gene expression. When these receptors are slowly reinstated after drug withdrawal, they may return in a slightly altered form. They may not be quite so efficient as before in increasing the actions of GABA, the natural 'calming' neurotransmitter. As a result, the brain may be generally less sensitive to GABA and the individual is left with heightened central nervous system excitability and increased sensitivity to stress. Molecular biologists point out that changes in gene expression can be very slow, or even

unable, to reverse. (The action of benzodiazepines at GABA receptors is explained more fully in the Manual).

Some people appear to be naturally more prone to anxiety than others. Brain imaging and pharmacological studies have shown that there is a decreased density (decreased numbers) and subsensitivity of brain GABA/benzodiazepine receptors in patients with generalised anxiety disorder and panic disorder and in patients with tinnitus, even if they have never been treated with benzodiazepines. Perhaps these individuals with genetically fewer GABA/benzodiazepine receptors are those more likely to experience long-term effects of benzodiazepines, protracted symptoms after withdrawal, and apparent recurrence of withdrawal symptoms.
Symptoms of a chronic hyperactive nervous system persisting after withdrawal are listed in the Manual Chapter 3, Table 3.

Benzodiazepine receptors: is there a natural benzodiazepine?

Readers may well ask: Why do we have specific benzodiazepine receptors in our brain? They have clearly not evolved over thousands and millions of years just to sit there and wait until Valium arrived! Most drugs that affect the brain act on receptors that are already there, and all of these drugs have subsequently been found to take the place of natural substances synthesised within the body. For example, the receptors for morphine react with natural endogenous endorphins and enkephalins, the physiological pain-killers; the receptors for cannabis are normally stimulated by natural substances called anandamides (named after the Sanskrit word ananda, which means "bliss"); nicotine in tobacco reacts with nicotine receptors for the natural neurotransmitter acetylcholine; all the psychotropic drugs like antidepressants and antipsychotics affect the receptor for natural neurotransmitters such as serotonin, noradrenaline and dopamine. The conclusion from such discoveries is that there must exist a natural benzodiazepine which normally modulates the activity of GABA at GABA/benzodiazepine receptors, like diazepam, and acts as an inborn, calming, sleep-inducing and anticonvulsant agent.

A search for the elusive natural benzodiazepine has been going on for about twenty years. Natural benzodiazepines have been found in plants, including potatoes, wheat, corn, rice, valerian and poppy and have also been demonstrated in animal tissues. Diazepam and its metabolite nordiazepam have been found in human blood and brain but these could have been derived from dietary sources. However, some substances which are not chemically related to benzodiazepine drugs but combine with GABA/benzodiazepine receptors have been found in the brain and other tissues of a variety of animals including rats, cattle, frogs, fish and humans and in isolated rat brain slices. These agents, which are small polypeptides, have been termed *endozepines* and are thought to be the body's natural benzodiazepines. They have a number of actions, among which is the ability to react specifically with the benzodiazepine site of the GABA-A receptor and to modulate GABA neurotransmission in the brain. Endozepines probably interact also with other types of GABA receptors which are distributed all over the body and have many functions.

There is still much to discover about endozepines. Some inhibit diazepam binding and may therefore be anxiogenic while others appear to act like diazepam and enhance GABA activity (as explained in the Manual, Chapter 1). It seems likely that the balance between different endozepines acting at the GABA-A receptor may determine an individual's susceptibility to anxiety and response to benzodiazepine drugs by acting as 'fine-tuners' of GABA-A function. The role of endozepines is still controversial but in my opinion natural benzodiazepines certainly exist, and they may already have been tracked down. Their presence adds to the complexity and sophistication of the brain. We know so little about what goes on in the brain, which makes it difficult to give advice on individual benzodiazepine problems.

Recurrence of symptoms after successful withdrawal

It is not unusual to experience recurrence of apparent benzodiazepine withdrawal symptoms years after a successful withdrawal and a return to normal health. The particular pattern of symptoms is unique to the individual, depending on his physical and psychological makeup, and no doubt on the innate density of his/her benzodiazepine receptors and the balance of his endozepines (see above). The experience of benzodiazepine withdrawal is deeply etched into the mind and memory of those who have been through it, and is actually physically present in the strength and connections of their neural synapses, as all memories are. These recurrent symptoms are all signs of GABA underactivity with its accompanying increased output of excitatory neurotransmitters, resulting in a hyperactive, hypersensitive central nervous system. The mechanism is exactly the same as that of benzodiazepine withdrawal, which is why the symptoms are the same.

In nearly every case of apparent recurrence, the precipitating cause for the return of symptoms turns out, on close inspection, to be an increase in environmental stress. The trigger may be a new stress or worry which may be unrecognised so that the return of symptoms seems to occur out of the blue. Contributing factors can be an infection, surgery, dental problems, work problems, fatigue, bereavement, family problems, loss of sleep, adverse reaction to a drug, change of environment - almost anything. It may also be that with increasing age and long-term worries, the brain simply gets less efficient at coping with stress. In addition, there may still be some lingering old disturbing worries/thoughts/memories that have been buried in the unconscious mind but are resurfacing now because the brain has not been able to deal with them adequately in the past. For those who have experienced a traumatic benzodiazepine withdrawal, an element of post-traumatic-stress disorder (PTSD) may be involved. This is a recurrent condition that can be triggered by small reminders of the past trauma. It is as if any new stress pushes the individual over the limits of his stress-coping abilities. As discussed above, some people who have been on long-term benzodiazepine treatment have a lowered tolerance to stress, even after they have stopped taking the drug, and are therefore more vulnerable to new or recurrent stresses.

It is not clear why many people report experiencing adverse effects from new drugs or drugs they have tolerated before taking benzodiazepines. The drugs involved are so disparate - from skin ointments to eye drops to local anaesthetics to antidepressants, steroids and many others - that it is difficult to attribute these reactions to metabolic effects, allergies or other known effects. Presumably the general hypersensitivity of the nervous system magnifies the reaction to any foreign substances, but no clear explanation has yet emerged. An exception is quinolone antibiotics which displace benzodiazepines from their binding sites and should not be taken by patients on, or recently on, benzodiazepines.

Reinstatement, updosing

A dilemma faced by some people in the process of benzodiazepine withdrawal, or after withdrawal, is what to do if they have intolerable symptoms which do not lessen after many weeks. If they are still taking benzodiazepines, should they increase the dose? If they have already withdrawn, should they reinstate benzodiazepines and start the withdrawal process again? This is a difficult situation which, like all benzodiazepine problems, depends to some degree on the circumstances and the individual, and there are no hard and fast rules.

Reinstatement after withdrawal? Many benzodiazepine users who find themselves in this position have withdrawn too quickly; some have undergone 'cold turkey'. They think that if they go back on benzodiazepines and start over again on a slower schedule they will be more successful. Unfortunately, things are not so simple. For reasons that are not clear, (but perhaps because the original experience of withdrawal has already sensitised the nervous system and heightened the level of anxiety) the original benzodiazepine dose often does not work the second time round. Some may find that only a higher dose partially alleviates their symptoms, and then they still have to go through a long withdrawal process again, which again may not be symptom-free.

Updosing during withdrawal? Some people hit a "sticky patch" during the course of benzodiazepine withdrawal. In many cases, staying on the same dose for a longer period (not more than a few weeks) before resuming the withdrawal schedule allows them to overcome this obstacle. However, increasing the dose until a longed-for plateau of 'stability' arrives is not a good strategy. The truth is that one never 'stabilises' on a given dose of benzodiazepine. The dose may be stable but withdrawal symptoms are not. It is better to grit one's teeth and continue the withdrawal. True recovery cannot really start until the drug is out of the system. Pharmacologically, neither reinstating nor updosing is really rational. If withdrawal symptoms are still present, it means that the GABA/benzodiazepine receptors have not fully recovered (see above). Further benzodiazepines cause further down-regulation, strengthen the dependence, prolong withdrawal, delay recovery and may lead to protracted symptoms. In general, the longer the person remains on benzodiazepines the more difficult it is to withdraw. On the whole, anyone who remained benzodiazepine-free, or has remained on the same dose, for a number of weeks or months would be ill-advised to start again or to increase dosage. It would be better to

devote the brain to solving individual symptoms and to finding sources of advice and support. Advice about how to deal with individual symptoms is given in the Manual (Chapter 3).

Nutritional supplements (added April 12, 2012)

There is no evidence that nutritional supplements such as vitamins, minerals, amino acids etc. are helpful in benzodiazepine withdrawal. Excessive doses of some can be toxic and others may even contain benzo-like substances that have the same adverse effects as benzodiazepines themselves. Nor is there any evidence that suggests benzodiazepine withdrawal causes vitamin, mineral or other deficiencies. No-one should take supplements without clear evidence of a specific deficiency. Those who advocate multiple supplements should first show evidence of any deficiency and then conduct proper controlled trials. In particular, taking GABA precursors does not increase GABA concentrations in the brain. Benzodiazepines do not decrease GABA concentrations; instead they alter GABA-receptor affinity. This slowly reverses without the need for supplements and there is no evidence that supplements speed the process. People taking or withdrawing from benzodiazepines should eat a normal healthy diet - which, after all, consists of "natural" substances and contains all the ingredients necessary for the body.

Some products which people have tried and found to be at best useless, at worst harmful include: mineral and vitamin supplements, valerian, St. John's Wort, kava-kava, melatonin, Rescue Remedy, BeCalm'd, choline, Noni juice, 5htp, SAMe and GABA. Most recently someone reported adverse effects from a product called Exhilarin (see Terri's Story).

Metabolism of benzodiazepines (added November 21, 2013)

It has long been known that there is a wide variation between individuals in the rate at which they metabolise psychotropic drugs, including benzodiazepines, antidepressants and antipsychotics. People can be poor or slow metabolisers, normal metabolisers, or extensive metabolisers for these drugs, depending on the genetically determined activity of certain drug metabolising enzymes (CYP450 2D6 enzymes). In particular, there appear to be more poor and slow metabolisers among Asian patients than in European populations, according to an important US study. This means that Asian patients respond to lower doses and experience more serious side-effects on standard doses of benzodiazepines than other ethnic groups. These days when multi-ethnic populations, including many people of Asian extraction, exist world-wide, doctors and psychiatrists may need to be reminded that in Asian patients, benzodiazepine (and antidepressant or antipsychotic) prescriptions, if considered necessary, should be started at half the standard dose in case they are poor or slow metabolisers.

Conclusion

The advice and explanations given in the Supplement may seem inadequate. They no doubt illustrate how much more we still need to know about benzodiazepines. However, it is important to remember that by far the greatest majority of long-term benzodiazepine users do recover from withdrawal - given time. Even protracted symptoms tend to decrease gradually, sometimes over years. The individual needs to know that the actual drug withdrawal is only the first step towards recovery. It may be followed by a prolonged period of convalescence during which the damage caused to the person's body - and often to his whole life - needs to be repaired as far as possible. But the brain, like the rest of the body, has an enormous capacity for adapting and self-healing. That is how life survives and how ex-benzodiazepine 'addicts' can be optimistic about their future.

Support & Contacts

The resources section from the original manual has been removed as it was out of date and many of the groups originally listed have since closed. Benzodiazepine Information Coalition has added the following up-to-date (as of 2019) resource list. Please note that Dr. Ashton does not endorse any support group.

For a current listing of support groups please visit www.benzoinfo.com/resources